Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Nivolumab

Proprietary Product Name: Opdivo

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

January 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ABMTRS	Australasian bone marrow transplant recipient society
ABVD	Adriamycin, bleomycin, vinblastine and dacarbazine
ADA	Anti-drug antibody
AE	Adverse event
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
Allo-SCT	Allogeneic stem cell transplant
BMS	Bristol-Myers Squibb
BOR	Best overall response
Bren	Brentuximab vedotin
BV	Brentuximab vedotin
cHL	Classical Hodgkin lymphoma
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CR	Complete remission
CRC	Colorectal carcinoma
CRF	Case report form
CSR	Clinical study report
DMC	Data monitoring committee
DOR	Duration of response
ECL	Electrochemiluminescence
ECOG	Eastern cooperative oncology group
EMA	European medicines agency
EFS	Event free survival

Abbreviation	Meaning
ER	Exposure-response
ESMO	European Society for Medical Oncology
EU	European union
FDA	United States Food and Drug Administration
FDG	Fluorodeoxyglucose
FFS	Failure free survival
GCP	Good clinical practice
HCC	Hepatocellular carcinoma
HL	Hodgkin lymphoma
HNSCC	Head and neck squamous cell cancer
HR	Hazard ratio
ICE	Isofamide, carboplatin, and etoposide
IEC	Independent ethics committee
IMAE	Immune mediated adverse event
irAE	Immune related adverse event
irAR	Immune mediated adverse reaction
IRB	Institutional review board
IRRC	Independent radiology review committee
IND	Investigational new drug
ISE	Integrated Summary of Clinical Efficacy
ISS	Integrated Summary of Safety
IV	Intravenous
IWG	International Working Group
LDH	Lactate dehydrogenase
LPFT	Last patient first treatment
Max	Maximum

Abbreviation	Meaning
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NCCN	National comprehensive cancer network
NHL	Non-Hodgkin lymphoma
Nivo	Nivolumab
NSCLC	Non-small cell lung cancer
NS	Not stated
NSQ	Non-squamous
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBS	Pharmaceutical benefits scheme
PBAC	Pharmaceutical benefits advisory committee
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PPK	Population pharmacokinetic(s)
PR	Partial remission
PrOR	Probability of achieving objective response
PT	Preferred term
Q2W	Every two weeks
QoL	Quality of Life

Abbreviation	Meaning
RCC	Renal cell carcinoma
r/R HL	Relapsed/refractory Hodgkin Lymphoma
SAE	Serious adverse event
sBLA	Supplemental Biologics License Application
SCS	Summary of Clinical Safety
SCE	Summary of Clinical Efficacy
SCLC	Small cell lung cancer
SCT	Stem cell transplant
SD	Stable disease, standard deviation
SQ	Squamous
TGA	Therapeutic goods administration
TNBC	Triple negative breast cancer
TTR	Time to response
US	United States
USPI	United States prescribing information
UTD	Unable to determine
WHO	World Health Oganization

1. Introduction

This is an application for an extension of indications to register Opdivo (nivolumab), for the treatment of patients with classical Hodgkin lymphoma (relapsed/refractory cHL).

1.1. Drug class and therapeutic indication

Nivolumab is a fully human anti-PD-1 monoclonal antibody (IgG4) produced by recombinant DNA technology and is the 'second in class' anti-PD-1 immune checkpoint inhibitor to be approved for use in Australia. Pembrolizumab, the first-in-class, was approved by the TGA in April 2015 for use in advanced melanoma.

In early 2016, the TGA approved the following indications for nivolumab:

- As monotherapy for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma.
- In combination with Yervoy (ipilimumab) for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH).
- As monotherapy for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy.
- As monotherapy for the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, OPDIVO should be used after progression on or after targeted therapy.

An additional NBE application is currently (as of September 2016) under evaluation by the TGA for the additional indication of:

- As monotherapy for the treatment of patients with advanced renal cell carcinoma after prior therapy in adults.

The proposed extension of indication for nivolumab in this submission is:

> *'Opdivo, as monotherapy is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) following after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin,*
>
> *or*
>
> *after following at least two prior therapies in patients who are not candidates for ASCT.'*

Comment: Inconsistent wording for the proposed indication is used in the sponsor's documents with 'following after' or 'following' or 'after' used in the cover letter, the PPF and the proposed PI respectively. The Clinical Overview uses slightly different wording again.

From the dossier, on the Declaration of Compliance with Pre-Submission Planning Form, the sponsor's preferred wording would appear to be:

> *'Opdivo, as monotherapy is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin,*
>
> *or*
>
> *after at least two prior therapies in patients who are not candidates for ASCT.'*

This is the wording that will be referred to in this Clinical Evaluation Report (CER), although the sponsor is asked to further clarify the wording of the proposed extension of indication.

The evaluator recommends that, if nivolumab is approved for the proposed indication, the indication wording should be changed to the following:

> *'Opdivo as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin,*
>
> *The approval for this indication is on the basis of objective response rate in 95 patients. Durability of response and any effects on progression free survival or overall survival have not been established.'*

Comment: The evaluator has recommended further revisions to the indication following the sponsor's responses to clinical questions regarding the Product Information (PI).

1.2. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

- Opdivo (nivolumab) 40 mg in 4 mL (10 mg/mL) concentrate solution for IV infusion vial
- Opdivo (nivolumab) 100 mg in 10 mL (10 mg/mL) concentrate solution for IV infusion vial

No new dosage forms or strengths are proposed.

2. Clinical rationale

2.1. Background

The sponsor has proposed an indication for the use of nivolumab in patients with late stage classical Hodgkin lymphoma. In support of this, the sponsor has provided interim results from two small exploratory studies.

2.1.1. Hodgkin Lymphoma

Hodgkin lymphoma (HL) is a relatively rare haematological malignancy. It is classified as either nodular lymphocyte predominant (NLPHL) or the more common 'classical HL'. According to the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, classic Hodgkin lymphoma (cHL) is a monoclonal lymphoid neoplasm (in most instances derived from B cells) composed of mononuclear Hodgkin and multinucleated Reed-Sternberg (R-S) cells residing in an infiltrate containing a variable mixture of non-neoplastic small lymphocytes, eosinophils, neutrophils, histiocytes, plasma cells, fibroblasts and collagen fibres. Neoplastic cells (R-S cells and Hodgkin cells) make up 0.1 to 1% of the tumour mass, with the bulk comprised of non-malignant cellular infiltrate. In nearly all cases of cHL, R-S cells express CD30, a glycoprotein belonging to the tumour necrosis factor receptor superfamily. There are four histological sub-types of classical HL: nodular sclerosing type (65%); mixed cellularity type (25%); lymphocyte-rich (4%); lymphocyte depleted (1%). The histological sub-type does not alter prognosis or management.

NLPHL makes up 5% of all HL and differs histologically from cHL in that R-S cells are not present. NLPHL is usually managed differently from classical HL and regarded as a separate disease.

2.1.1.1. Assessing tumour response

The International Working Group criteria for malignant lymphoma are commonly used to assess response to treatment in clinical trials.[1] These criteria were originally developed to assess response to cytotoxic chemotherapeutic agents and were first described 1999. The criteria (shown in Table 1, below) were revised in 2007 such that application of the criteria involved both CT and PET scanning. Use of the criteria in assessing tumour response is complex, as shown by the response definitions in the figure below. The reliability of these criteria in the setting of immunotherapy, where there is the phenomenon of 'pseudoprogression' (described below) is not established.

Table 1. International Working Group response definitions from clinical trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR (Complete remission)	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR (Partial remission)	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD (Stable disease)	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET; (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		

[1] Cheson, B, et al. Revised Response Criteria for Malignant Lymphoma. 2007. J Clin Oncol;25(5): 579-86.

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
Relapsed disease or PD (Progressive disease)	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

2.1.1.2. Treatment of HL

HL usually responds well to frontline therapy: 90% of patients with 'classical' or localised disease and 30% of patients with disseminated HL have a curative response. For those 10-20% of patients with HL who do not respond to front-line therapy or who relapse following an initial response to frontline therapy (relapsed/refractory HL, r/r HL), the treatment of choice consists of high-dose 'salvage' chemotherapy followed by autologous stem cell transplantation (ASCT). Salvage chemotherapy regimens such as dexamethasone/high-dose Ara-C/cisplatin (DHAP), ifosfamide/gemcitabine/vinorelbine (IGEV) or ifosfamide/carboplatin/etoposide (ICE) are given to reduce the tumour burden and determine eligibility for ASCT. Patients with lack of response to salvage chemotherapy or with significant organ disease and/or poor performance status are usually not considered eligible.

2.1.1.3. Relapse following ASCT

Approximately 50% of patients may relapse following ASCT. Risk factors for progression following ASCT have been extensively studied to identify patients most likely to benefit from ASCT. Pre-ASCT risk factors consistently reported to be associated with relapse or refractory disease post-ASCT include primary refractory Hodgkin's lymphoma, initial remission duration of less than 12 months, Ann Arbor stage III or IV at relapse, presence of extra-nodal or advanced-stage disease at time of relapse, presence of B symptoms, lack of response to pre-transplantation salvage chemotherapy, and residual disease pre-ASCT (defined by CT or PET scans).

A variety of prognostic indices have been proposed but no universal agreement has been reached. These indices commonly divide patients into low, intermediate or high risk groups according to the number of risk factors present (for example, 0 or 1, 2, 3 or more risk factors respectively). The outcomes in patients who develop progressive disease following ASCT have been shown to vary according to the number of pre-ASCT risk factors and have been consistently worse if two or more risk factors are present (intermediate to high risk). The 5 year OS for patients has been variably reported as 80 to 100% for low risk, 55 to 85% for intermediate risk and 13 to 57% for high risk.

The outcomes for patients with relapsed/refractory cHL following ASCT have improved with the use of brentuximab vedotin. A Phase II study recently found brentuximab vedotin to be relatively safe and efficacious in patients who relapse following ASCT, resulting in approval for this indication in a number of jurisdictions, including Australia.[2] The published 3 year follow-up results of this study (Gopal 2015) of 102 patients reported that 48/102 patients were still alive

[2] Australian Public Assessment Report (AusPAR) for brentuximab vedotin; Proprietary Product Name: Adcetris. Sponsor: Takedo Pharmaceuticals Australia Pty Ltd. Date of AusPAR May 2014. Therapeutic Goods Administration (TGA); Canberra, Australia.

with 18 patients still in remission. The estimated median OS for all patients was 40.5 months (95% CI: 28.7, upper bound not reported) and the estimated PFS per investigator for all patients was 9.3 months. Outcomes with the use of brentuximab vedotin for relapse/refractory HL following ASCT outside prospective clinical trials have been recently reported (see Table 2, below).[3]

Table 2. Review of published named patient programs with brentuximab vedotin in patients having primary refractory or relapsed Hodgkin's lymphoma

NPP	Number of Patients	Age in Years (Median)	Primary Refractory Disease (%)	Previous SCT (%)	Median BV Cycles	ORR (%)	CR (%)	PFS (Months)	OS (%) (Months)
Rothe et al. 2012[12]	45	35	62	87	7	60	22	8	83 (12)
Gibb et al. 2013[13]	18	41.5	NA	33	5.5	72	17	5.1	NA
Zinzani et al. 2013[14]	65	27.5	69.2	87.7	8	70.7	21.5	6.8	73.8 (20)
Salihoglu et al. 2014[15]	58	26	49	79.6	7	63.5	26.5	7	70.6 (12)
Yang et al. 2014[16]	22	30	54.5	77.3	5	72.7	18.2	5.7	NA

BV = brentuximab vedotin; CR = complete response; NA = not available; NPP = Named Patient Program; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SCT = stem cell transplantation.

There is limited information to guide management of patients who relapse following brentuximab vedotin and ASCT. Generalisation from information regarding relapse following ASCT would suggest that these patients are often young, without comorbidities and able to tolerate additional therapies. Treatment options may include single agent or combination chemotherapy, re-treatment with brentuximab vedotin, repeat ASCT, radiation and allogeneic stem cell transplant (allo-SCT). Responses may, however, be short lived with patients progressing through a sequence of therapies. From recent estimates median survival for patients receiving one or more of these treatment options is considered to be around 2 years.

The sponsor has provided two early phase single arm studies to support the proposed indication. Assessment of the clinical relevance of the results of these studies requires comparison to historical controls. A recent review article describes outcomes with single agent chemotherapy, combination agent chemotherapy and novel agent regimens in patients with relapsed/refractory cHL after ASCT (see Tables 3 to 5, below).[4] The article notes that the use of combination chemotherapy was associated with an increased risk of myelosuppression and secondary malignancy such as AML or MDS. Many of the studies presented were retrospective single centre studies. These showed objective response rates that were mainly around 50 to 70% for conventional treatment lines with progression free survival ranging from 5months to 14 months. The reported ORRs with novel agents tended to be lower, except for brentuximab vedotin, nivolumab and pembrolizumab. The PFS with these treatments ranged from 5 to 8 months.

[3] Domingo-Domenech E, et al. Brentuximab Vedotin in Relapsed/Refractory Hodgkin's Lymphoma. European Oncology & Haematology, 2015;11(1):21–4.

[4] Alinari L, Blum KA. How I treat relapsed classical Hodgkin Lymphoma after autologous stem cell transplant. Blood 2016 127:287-295.

Table 3. Outcomes of selected studies using single or combination agent chemotherapy regimens in patients with relapsed/refractory cHL

Agent	No. of Patients	Prior ASCT	Response, %	PFS, mo	Reference
Gemcitabine	27	18	ORR, 22 PR, 22	6.4	37 38 39
Vinblastine	17	17	ORR, 59 CR, 12 PR, 47	EFS, 8.3	40
Vinorelbine	24	NR	ORR, 50 CR, 14 PR, 36	6	41
Bendamustine	34	26	ORR, 53 CR, 33 PR, 20	5.2	42
Liposomal doxorubicin	47	31	ORR, 72 CR, 51 PR, 21	NR	43

Other agents with single-agent activity in cHL include chlorambucil, vincristine, etoposide, cyclophosphamide.
NR, not reported.

Table 4. Selected clinical studies on treatment options with combination regimens in patients with relapsed/refractory cHL after ASCT

Agent	No. of patients	Median no. of prior therapies (range)	Prior ASCT	Median no. of cycles given (range)	Response, %	PFS	Reference
GVD	91	1 (NR)	36	2-6	ORR, 70 CR, 19 PR, 51	EFS 8.5 mo (prior ASCT group)	44
GemOx	24	2 (1-6)	10	4 (1-12)	ORR, 71 CR, 38 PR, 33	14 mo	45
GV	8	3 (1-11)	8	2 (2-4)	ORR, 75 CR, 50 PR, 25	NR	46
GCD	14	2 (1-8)	4	4 (1-4)	ORR, 86 CR, 50 PR, 36	NR	47
ESHAP	22	≥1 (NR)	2	4 (1-6)	ORR, 73 CR, 40 PR, 33	3-y 27%	48
GDP	23	1	0	2 (2-3)	ORR, 69 CR, 17 PR, 52	NR	49
DHAP	102	1	0	2	ORR, 88 CR, 21 PR, 67	18-mo FFTF 54%	50
ICE	13	1 (1-4)	0	2 (2-3)	ORR, 100 CR, 31 PR, 69	30-mo 69%	51 52
IGEV	91	1 (1-4)	0	4	ORR, 81 CR, 54 PR, 27	3-y 53%	53
ASHAP	56	1	0	2	ORR, 70 CR, 34 PR, 36	4-y EFS 36%	54
ChlVPP	100	0 (0-1)	0	6	ORR, 94 CR, 88 PR, 6	3-y 76%	55 56 57

Other combination regimens with potential activity in cHL include cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (EPOCH).
ASHAP, doxorubicin, methylprednisolone, cytarabine, cisplatin; ChlVPP, etoposide, methylprednisolone, chlorambucil, vinblastine, procarbazine prednisone; GCD, gemcitabine, carboplatin, dexamethasone; GDP, gemcitabine, dexamethasone, cisplatin; GemOx, gemcitabine, oxaliplatin; GV, gemcitabine, vinorelbine; ICE, ifosfamide, carboplatin, etoposide; IGEV, ifosfamide, gemcitabine, vinorelbine; NR, not reported.

Table 5. Outcomes of selected studies using novel agents in patients with relapsed/refractory cHL

Agent	No. of patients	Prior ASCT	Response, %	PFS	Reference
Brentuximab	102	102	ORR, 75 CR, 34 PR, 41	5.6 mo	28
Nivolumab	23	18	ORR, 87 CR, 17 PR, 70	24-wk 86%	29
Pembrolizumab	15	10	ORR, 53 CR, 20 PR, 33	NR	30
Lenalidomide	36	31	ORR, 19 CR, 3 PR, 16	6 mo	31 58 59
Rituximab	22	18	ORR, 22 CR, 4.5 PR, 18	7.8 mo	60
Everolimus	19	16	ORR, 47 CR, 5 PR, 42	7.2 mo	32
Vorinostat	25	11	ORR, 4 CR, 0 PR, 4	4.8 mo	61
Panobinostat	129	129	ORR, 27 CR, 4 PR, 23	6.1 mo	33

Note: The nivolumab result above is from a published article based on Study CA209039 and is based on the ORR per investigator. The ORR per IRRC performed retrospectively was 60%.

Allogeneic stem cell transplant is an important treatment option as it is potentially curative. However, clinical use is limited due to low long-term PFS rate of 20% to 30% and high rates of morbidity and treatment-related mortality (20 to 60%). Reduced intensity conditioning (RIC) allo-SCT has been developed in the hope of reducing treatment related mortality without compromising efficacy. A recent Phase II study described 78 patients with relapsed HL who were treated with induction chemotherapy followed by RIC allo-SCT.[5] This study found that allograft-related mortality was 8% at 100 days and 17% at 2 years; after median follow-up of 32 months, the estimated PFS rate was 48% at 1 year and 24% at 4 years; and after a median follow-up of 48 months, 33 patients were still alive (43%). The estimated overall survival rate was 71% (95% CI, 67 to 76%) and 43% (95% CI, 39 to 46%) at 1 and 4 years, respectively.

2.1.1.4. Clinical guidelines for relapsed/refractory cHL following ASCT

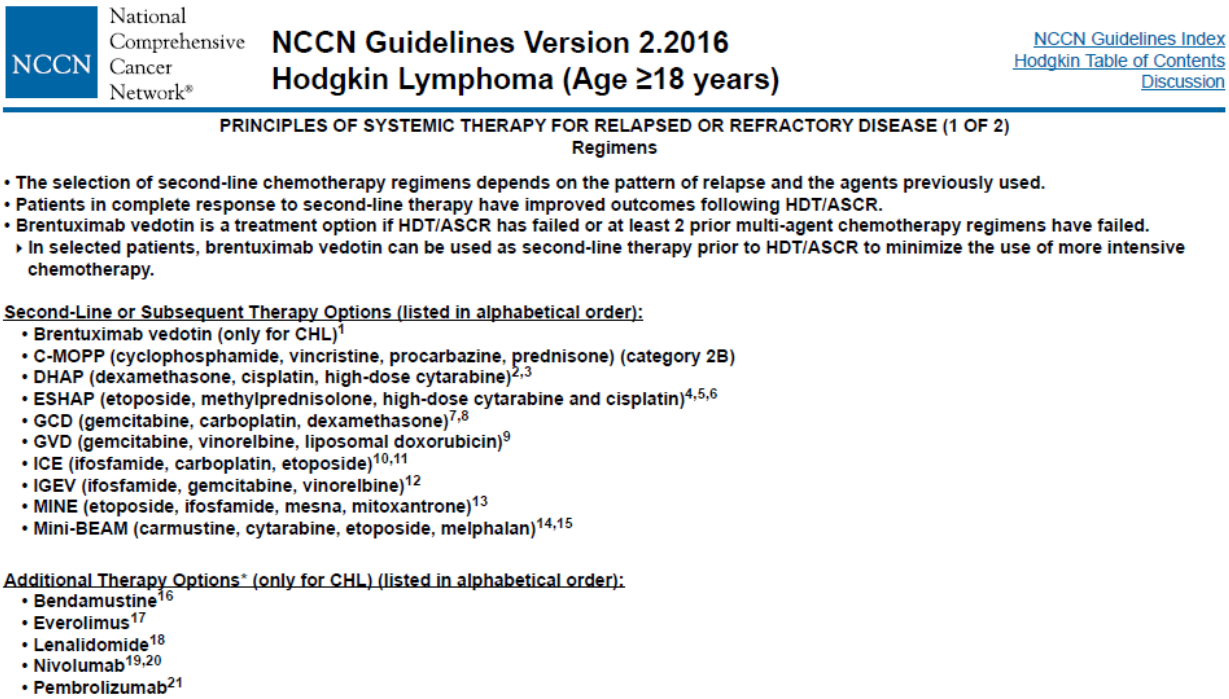
Despite the variety of treatment options that have been used in patients who relapse following ASCT, widely accepted clinical guidelines do not make clear recommendations regarding the ranking of these options. The 2014 ESMO guideline recommends single agent brentuximab vedotin with alternative options of enrolment in a clinical trial evaluating novel agents, allogeneic stem cell transplant, palliative single agent chemotherapy with gemcitabine or bendamustine and/or radiotherapy.[6] The 2016 National Comprehensive Cancer Network

[5] A. Sureda, et al., Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study: a prospective clinical trial by the Grupo Español de Linfomas/Trasplante de Médula Osea (GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation,' Haematologica, vol. 97, no. 2, pp. 310–317, 2012.

[6] Eichenauer D. Hodgkin's Lymphoma: ESMO Clinical Practice Guidelines. Ann Oncol (2014) 25 (suppl 3): iii70-iii75.

guidelines for Hodgkin Lymphoma state that brentuximab vedotin is a treatment option if ASCT has failed, or at least 2 prior multi-agent chemotherapy regimens have failed (see Figure 1, below). A number of chemotherapy options are listed for relapsed or refractory disease but no specific recommendations are made. Of note is that a number of immune modulators, including nivolumab, are listed in 'Additional Therapy Options (for cHL)'.

Figure 1. Excerpt from the NCCN Guideline for Hodgkin lymphoma



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Hodgkin Lymphoma (Age ≥18 years)

NCCN Guidelines Index
Hodgkin Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSED OR REFRACTORY DISEASE (1 OF 2)
Regimens

- The selection of second-line chemotherapy regimens depends on the pattern of relapse and the agents previously used.
- Patients in complete response to second-line therapy have improved outcomes following HDT/ASCR.
- Brentuximab vedotin is a treatment option if HDT/ASCR has failed or at least 2 prior multi-agent chemotherapy regimens have failed.
  - In selected patients, brentuximab vedotin can be used as second-line therapy prior to HDT/ASCR to minimize the use of more intensive chemotherapy.

Second-Line or Subsequent Therapy Options (listed in alphabetical order):

- Brentuximab vedotin (only for CHL)[1]
- C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) (category 2B)
- DHAP (dexamethasone, cisplatin, high-dose cytarabine)[2,3]
- ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin)[4,5,6]
- GCD (gemcitabine, carboplatin, dexamethasone)[7,8]
- GVD (gemcitabine, vinorelbine, liposomal doxorubicin)[9]
- ICE (ifosfamide, carboplatin, etoposide)[10,11]
- IGEV (ifosfamide, gemcitabine, vinorelbine)[12]
- MINE (etoposide, ifosfamide, mesna, mitoxantrone)[13]
- Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)[14,15]

Additional Therapy Options* (only for CHL) (listed in alphabetical order):

- Bendamustine[16]
- Everolimus[17]
- Lenalidomide[18]
- Nivolumab[19,20]
- Pembrolizumab[21]

2.1.2. Brentuximab vedotin

Brentuximab vedotin has been recently approved by the TGA for indications similar to those proposed for nivolumab. In December 2013, brentuximab vedotin was approved for the indications of:

> *'Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):*
>
> *following autologous stem cell transplant (ASCT) or*
>
> *following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option*
>
> *Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).'*

Brentuximab vedotin (Adcetris) is an anti-neoplastic agent active against CD30-expressing cells, including Hodgkin's and Reed-Sternberg cells in Hodgkin's lymphoma.

Brentuximab vedotin is an antibody drug conjugate (ADC) consisting of three components: an IgG1 antibody cAC10, specific for the human cell membrane receptor CD30, the microtubule disrupting agent monomethyl auristatin E (MMAE) and a protease cleavable linker that covalently bonds MMAE to cAC10. Its biological activity is thought to result from a multi-step process with binding of the antibody to the receptor CD30 on the cell surface followed by internalization of the ADC-CD30 complex with intra-cellular release of MMAE and subsequent disruption of the microtubule network, inducing cell cycle arrest and apoptotic death of the cell. Adverse events reported with brentuximab vedotin, including peripheral neuropathy, are attributed to free MMAE with this thought to result from leakage from CD30+ cells or other sites of metabolism of the ADC.

According to the Australian Public Assessment Report for brentuximab vedotin, TGA approval for the indication of use in adult patients *with relapsed or refractory CD30+ Hodgkin lymphoma (HL) following ASCT* was based on a single arm multicentre Phase II study of 102 patients who received brentuximab vedotin 1.8 mg/kg IV once every 3 weeks, for up to 16 infusions.[2] Analysis after median follow-up of 9 months showed an objective response rate (ORR) of 75%.[7] Longer term follow-up of the study has since been published.[8,9]

There were concerns expressed by regulatory bodies regarding the strength of this Phase II open label study and whether it was adequate to demonstrate efficacy. According to the Australian Public Assessment Report for brentuximab vedotin, the TGA asked that the ACPM advise on whether '*evidence from Phase II, uncontrolled studies sufficient to proceed with registration*'.[2] The ACPM advice was that: '*The ACPM was of the view that the very favourable benefit-risk ratio of brentuximab monotherapy in Phase II trials for the proposed indications was adequate evidence'* although *'the primary endpoint of overall response rate (ORR) was not ideal'.* The EMA's CHMP queried whether, for convincing evidence of efficacy, a controlled study was required and convened a Scientific Advisory Group for Oncology to address this concern.[10] This group advised that the observed anti-tumour activity of brentuximab vedotin was considered clinically relevant due to the high response rate and duration of response.

2.1.2.1. Brentuximab vedotin in patients with relapsed CD30+ HL who are not candidates for ASCT

The proposed indication proposes nivolumab as an alternative to brentuximab vedotin in patient with relapsed cHL in whom ASCT is not appropriate. According to the Australian Public Assessment Report for brentuximab vedotin, TGA approval for the indication of *adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option* was based on 2 Phase I, single arm, open label, dose escalation studies that enrolled patients with HL who had failed systemic chemotherapy induction or salvage and were ineligible for, refused treatment by or previously had had an ASCT or whom had sALCL.[2] For the 20 or so patients from both studies who had not received prior ASCT, the ORR was 30%. The EMA's assessment included a larger dataset of 40 HL patients who had not received prior ASCT (and who were treated at 1.8 mg /kg three weekly), from Studies 0001, 0002 and other sources. In this larger population the ORR was 55% (including 22.5% CR, and also including 20% who went on to SCT). According to the CHMP assessment, anti-tumour activity was considered to be established by the response rates.[10] This was considered clinically relevant as the treatment might offer the opportunity of obtaining a complete response or the option for subsequent potentially curative stem cell transplantation.

A number of small retrospective audits have also suggested that brentuximab vedotin may be efficacious in this setting, including providing a bridge to potentially curative ASCT:

[7] Younes A, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol. 2012 Jun 20;30(18):2183-9.

[8] Gopal et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood. 2015;125(8):1236-1243.

[9] Five-Year Survival Data Demonstrating Durable Responses from a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory Hodgkin Lymphoma (Abstract 2736, poster presentation on Sunday, December 6, 2015).

[10] Gravanis I et al. The European Medicines Agency Review of Brentuximab Vedotin (Adcetris) for the Treatment of Adult Patients with Relapsed or RefractoryCD30+ Hodgkin Lymphoma or Systemic Anaplastic Large Cell Lymphoma: Summary of the Scientific Assessment of the Committee for Medicinal Products for Human Use. The Oncologist 2016;21:102-109. Reference provided by the sponsor.

- Viviani S, et al (2014): 16 patients with r/R CD30+ HL who were not suitable for ASCT received a median of 6 cycles of brentuximab vedotin. The ORR was 87.5%, with CR in 8 patients. Three patients subsequently underwent ASCT.[11]
- Holmberg L, et al (2013): 15 patients with CD30+ HL who did not respond to salvage chemotherapy received a median of 4 cycles of brentuximab vedotin. The ORR was 53% with 7/15 becoming FDG-PET negative and 1 achieving PR. Thirteen patients subsequently underwent ASCT. At median follow-up of 485 days post last dose of brentuximab vedotin, 14/15 patients were alive and 8/15 were disease free.[12]
- Sasse et al (2013): 14 patients with r/R CD30+ HL (9 with primary refractory disease) who were unsuitable for ASCT were treated with brentuximab vedotin. The ORR was 71%, with 5 patients achieving CR. Four patients subsequently underwent ASCT. The median PFS was 9 months and median OS was not yet reached.[13]
- Zinzani L, et al (2015): 30 patients with r/R CD30+ HL who did not respond to salvage chemotherapy received a median of 4 cycles of brentuximab vedotin. 9/30 patients became FDG-PET scan negative and progressed to ASCT.[14]

2.1.2.2. Brentuximab vedotin as consolidative therapy after ASCT for CD30+ HL

Brentuximab vedotin has also been investigated as consolidative therapy in patients receiving ASCT for relapsed or refractory Hodgkin lymphoma.[15] On the basis of the results of this randomised, double blind, placebo controlled Phase III study of SGN35 and best supportive care (BSC) versus placebo and BSC in the treatment of patients at high risk of residual Hodgkin Lymphoma following ASCT study, FDA approval for the indication 'Classical HL at high risk of relapse or progression as post-auto-HSCT consolidation' was granted on 17 August 2015. According to publically available documents, an application for a similar indication has been made to the EMA. This received a positive recommendation from the CHMP on 26 May 2016, after a lengthy evaluation, but has yet to be approved by the EMA (as of 23 July 2016).

2.1.3. Nivolumab and checkpoint inhibitors

Nivolumab is a fully human anti-PD-1 monoclonal antibody (IgG4) produced by recombinant DNA technology and second-in-class of the PD-1 pathway checkpoint inhibitors. It is believed to exert its anti-neoplastic effect by blocking the co-opting of the PD-1 pathway by tumours to avoid an immune response.

The complex interactions between tumours and the human immune system are not fully understood. It is believed that there is a process of 'immune surveillance' by which the immune system can identify cancerous and/or precancerous cells, through the expression of tumour-specific antigens or molecules induced by cellular stress, and eliminate them before they can cause harm.[16] Current thinking is that malignant tumour progression and growth may occur

[11] Viviani S, et al. Brentuximab Vedotin (BV) an Effective Treatment for Autologous (ASCT) and/or Allogeneic (alloSCT) Transplant naïve Patients with Relapsed/Refractory (R/R) Hodgkin Lymphoma (HL): A retrospective Single-Institution Study Blood Dec 2014, 124 (21) 5428.
[12] Holberg L, et al. Brentuximab Vedotin Administered To Platinum-Refractory Transplant Naïve Hodgkin Lymphoma Patients Can Increase The Proportion Achieving FDG-PET Negative Status. Blood 2013 122:2106.
[13] Sasse et al. Brentuximab vedotin (SGN-35) in patients with transplant-naive relapsed/refractory Hodgkin lymphoma. Leukaemia and Lymphoma Vol 54, Issue 10, 2013.
[14] Zinzani L, et al. Brentuximab Vedotin in Transplant-Naïve Relapsed/Refractory Hodgkin Lymphoma: Experience in 30 Patients. Oncologist. 2015 Dec;20(12):1413-6.
[15] Moskowitz et al. Brentuximab vedotin as consolidation therapy after autologous stem cell transplantation in patients with Hodgkin's Lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2015; 385: 1853-62.
[16] Swann J, Smyth M. Immune surveillance of tumors. Journal of Clinical Investigation. 2007;117(5):1137-1146.

through mechanisms that enable tumour cells to 'hide' from this immune surveillance, thereby avoiding immune system mediated destruction. One of these mechanisms involves tumour cell-surface expression of one or more of a series of molecules that effectively limit T-cell proliferation and killing capacity. These molecules are referred to as 'immune checkpoints' and their natural function is to restrain or dampen excessive immune responses.

One such check-point is the interaction between the Programmed Cell Death Ligands (PD-L1 and PD-L2) and the Programmed Cell Death-1 (PD-1) receptor. Activated T-cells express PD-1 on their surface and produce interferons that lead to the expression of PD-L1 in multiple tissues. Binding of PD-1 to its ligands, PD-L1 and PD-L2, inhibits effector T-cell activity and protects normal cells that express PD-L1 or PD-L2 from immune- mediated cell death. Teleologically, this interaction is believed to be an inhibitory pathway that helps to prevent overstimulation of immune responses and contributes to the maintenance of immune tolerance to self-antigens.

Aberrant expression of PD-L1 or PD-L2 on tumour cells is believed to limit and inhibit the anti-tumour immune response, enabling immune evasion by the tumour cells. Tumour PD-L1 membrane expression can be constitutive, through oncogenic processes, or induced by activated tumour antigen-specific T cells that produce interferons.

Blockade of PD-1, or the ligands, is thought to result in disinhibition of native immune responses and may re-activate anti-tumour immunity. This is thought to occur through restoring T-cell responsiveness and the ability to mount a direct T-cell immune attack against tumour cells. A number of therapeutic antibodies that inhibit the PD-1 pathway by blocking either PD-1 or PD-L1 are being developed for clinical use in a variety of tumour types. These include the PD-1 antibodies, nivolumab and pembrolizumab, and the PD-L1 antibody, atezolimumab. PD-1 antibodies block interactions between PD-1 and both PD-L1 and PD- L2, whereas anti-PD-L1 antibodies block the PD-1: PD-L1 interaction only.

Unlike conventional chemotherapy drugs that may result in a decrease in tumour size over weeks, immune checkpoint inhibitors can take several months to have this effect. These drugs can also cause an initial increase in tumour size ('pseudoprogression'), with this presumed due to infiltration of the tumour by activated T cells, other immune system cells and the associated inflammatory effect. This initial increase in size may be followed by shrinking or eradication of the tumour. Assessment of solid tumour response using standard criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) may result in over-diagnosis of 'tumour progression'. This has prompted development of different criteria for the assessment of solid tumour response to immunotherapy, 'immune related response criteria (irRC)'.[17] Similar criteria have not been developed for haematological malignancies.

Hodgkin lymphoma is considered to be a suitable target for PD-1 immune checkpoint inhibitors due to the extensive, but ineffective inflammatory and immune cell infiltrate, that surrounds Reed-Sternberg (R-S) cells within the tumours and due to high levels of expression of PD-L1 ligand by R-S cells. PD-1 ligand deregulation and overexpression in cHL has a genetic basis: chromosome 9p24.1/PD-L1/PD-L2 alterations increase the abundance of the PD-1 ligands, PD-L1 and PD-L2, and their further induction through Janus kinase 2 (JAK2)–signal transducers and activators of transcription signalling.[18] In addition, Epstein-Barr virus, found in some cases of cHL, also increases the expression of PD-L1.

2.1.3.1. Checkpoint inhibitors and regulatory approval

Checkpoint inhibitors have rapidly entered clinical practice. Ipilimumab was the first to receive regulatory approval in the US, Europe, Australia in 2011. Ipilimumab acts on the CTLA-4 pathway rather than the PD-1 pathway but also modulates T-cell function. The PD-1 receptor

[17] Wolchok J, et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria Clin Cancer Res December 1, 2009 15:7412-7420.

[18] Roemer M, et al. PD-L1 and PD-L2 Genetic Alterations Define Classical Hodgkin Lymphoma and Predict Outcome. JCO JCO664482.

antibody, pembrolizumab, was granted breakthrough designation by the FDA in 2013 and initially received accelerated approval for advanced melanoma followed by full approval, on the basis of confirmatory studies, in December 2015. It was also approved by the EMA and TGA in mid-2015.

Nivolumab entered clinical trials in patients with cancer in late 2007. Evidence of clinical activity in multiple tumour types was noted in the initial dose-escalation study, in which the drug was administered in an intermittent schedule. Phase III studies in melanoma, squamous and non-squamous NSCLC and renal cell carcinoma have since been completed. Nivolumab was approved for use in advanced melanoma, advanced squamous non-small cell lung carcinoma (NSCLC), and advanced non-squamous NSCLC by the FDA, EMA and TGA in 2015 to 2016. It has subsequently been approved for use in advanced renal cell carcinoma (November 2015) and classical HL (May 2016) by the FDA and for advanced renal cell carcinoma (May 2016) by the EMA. Combination therapy with ipilimumab for advanced melanoma has been approved by the FDA, EMA and TGA. Atezolizumab is a more recent checkpoint inhibitor to receive regulatory approval, receiving accelerated approval by the FDA for the treatment of urothelial carcinoma in May 2016.

2.1.3.2. Checkpoint inhibitors and immune related adverse events

The PD-1 pathway is believed to have an important role in maintaining immunologic homeostasis and immune tolerance to self-antigens. The use of checkpoint inhibitors has been associated with a unique spectrum of toxicities termed 'immune related adverse events' (irAEs) that are very different from toxicities observed with conventional cytotoxic chemotherapy.

The development of irAEs is believed to be a 'class effect' of checkpoint inhibitors and have included, to date, pneumonitis, colitis, encephalitis, toxic epidermal necrolysis, hepatitis, hypophysitis, adrenal failure, diabetes, myasthenia gravis/myasthenic syndrome, Guillian-Barre syndrome, severe infusion reactions, uveitis, myocarditis, rhabdomyolysis and thyroiditis. Fatal outcomes have been reported with most of these reactions. More severe and frequent irAE have occurred when combination immunotherapy is used, such as nivolumab and ipilimumab for advanced melanoma. Given the rapidity with which checkpoint inhibitors have entered clinical practice, and the limited number of patients exposed in the registration trials, identification of other irAEs and better understanding of the spectrum of severity with monotherapy can be expected with wider use. Familiarity of clinical staff with irAEs can be expected to be limited at this early stage of the use of immunotherapies.

Small numbers of publications describing the use of checkpoint inhibitors outside clinical trials are now appearing in the literature.[19,20] These articles describe the experience and lessons learnt in single centres using immunotherapies, together with a review of the literature. Common themes in these articles are that:

- irAEs represent a unique profile of side effects which are different from the chemotherapy-associated AEs
- irAEs may affect a variety of organs and may present in a non-specific and unpredictable fashion, necessitating proactive monitoring for early suspicion and investigation
- Prompt recognition and initiation of appropriate management usually results in complete reversibility, but failing to do so can lead to severe toxicity or even death
- Management of irAEs may involve symptomatic treatment, hormonal replacement, dose delay/withdrawal and immunosuppression

[19] Fay A, et al. (2016) The management of immune-related adverse events associated with immune checkpoint blockade, Expert Review of Quality of Life in Cancer Care, 1:1, 89-97.
[20] Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Translational Lung Cancer Research. 2015;4(5):560-575.

- Education of both clinicians and patients is an essential component of management to ensure awareness of irAEs, their timely recognition and appropriate management.

Development of guidelines regarding the use of immunotherapies and proactive monitoring for irAEs has lagged behind the spread of these treatments into clinical practice. For example, in June 2016, the Australian Cancer Treatments Online website, eviQ (eviQ.com.au), provides protocols for the use of brentuximab vedotin, pembrolizumab and ipilimumab but not for nivolumab. Also of note is that irAEs have not been included in the section Oncological Emergencies, although they are discussed in the separate protocols for pembrolizumab and ipilimumab, including the following statements:

- For ipilimumab: 'Review for toxicities every 3 weeks, before a dose is due. It is very important that the patient is educated to immediately report any key signs or symptoms to the treating oncology team'
- For pembrolizumab: 'Before commencing pembrolizumab treatment in any patient, clinicians should have an understanding of the common immune-related adverse events (irAEs) associated with pembrolizumab and their management.'

There is little advice available at other websites: the NCCN guidelines and ESMO guidelines for supportive care do not include irAEs. In the rapidly evolving clinical use of immunotherapies, the sponsor's PI becomes a critical source of information for clinical staff.

Comment: A guideline for the management of irAEs has since been provided on the eviQ website. According to the reference list, this guideline relies heavily on the Opdivo (nivolumab) Immune-Mediated Adverse Reactions Management Guide and PIs for nivolumab and ipilimumab.

The potential lack of familiarity of both patients and clinicians with irAE and the impact of this on their management has also been of concern to regulatory bodies. The EMA required an educational programme, physician educational material and a patient alert card with marketing approval of nivolumab. The Australian Specific Annexe of the draft RMP provided with the submission (Version 4.0) states: '*In Australia, additional risk minimization activities as per the EU-RMP consist of a healthcare provider (HCP) communication tool and a patient communication tool, to facilitate safe and effective use of nivolumab in the post-marketing setting.'* These tools were not included in this dossier but were provided during the Round 2 evaluation of the submission for use in advanced renal cell carcinoma that was occurring concurrently with this submission and have been extensively commented on in the Round 2 CER for that submission. Changes proposed to the tools are the subject of ongoing discussions between the TGA and the sponsor.

Given that most experience and clinical use of nivolumab to date has occurred through the sponsor's clinical development programme, the sponsor's documentation, including the tools above, is a vital source of information for clinicians and patients regarding irAE. It is essential that this documentation be appropriately detailed and be available to all clinicians who may be involved in the care of patients treated with nivolumab. It is important to note that, although patients may receive the actual drug treatment in specialist oncology centres, they may present elsewhere for emergency care, with this including the local GP or emergency department. Ongoing care for severe irARs may also be provided outside specialist oncology centres, due to distance or bed availability limiting patient transfer.

2.1.3.3. Pre-existing auto-immune disease and checkpoint inhibitors

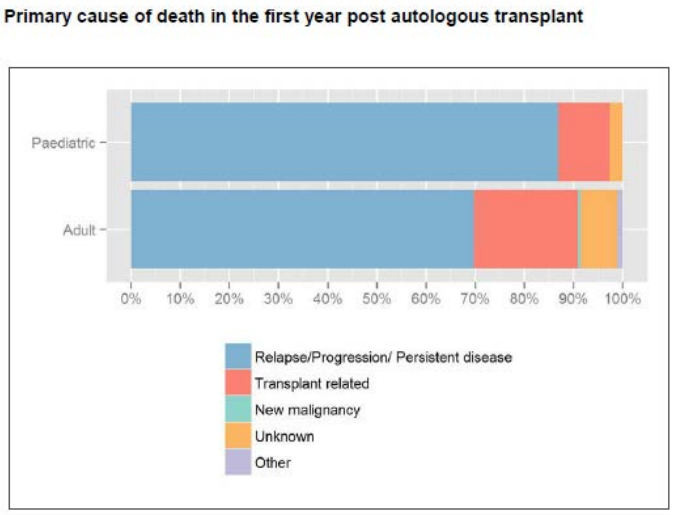
The safety of checkpoint inhibitors in patients with an underlying autoimmune condition is uncertain. There is theoretical concern that therapeutic blockade of these receptors could lead to exacerbations of underlying autoimmune conditions. These patients have been excluded from most clinical trials of immunotherapy.

2.1.4. HL and ASCT in Australia

The overall incidence for HL in Australia was 2.7 cases per 100,000 people in 2011, increasing from 2.2 cases per 100,000 people in 1982. The age distribution of incidence is bi-modal with a peak in young adults aged 15 to 34 years and a further peak observed in older adults aged 60 to 80 years. Approximately 550 to 600 new diagnoses of HL are made per year and approximately 60 deaths due to HL are reported per year.[21]

The Australasian Bone Marrow Transplant Recipient Society maintains a registry of patients who are treated with bone marrow, peripheral blood and cord blood stem cell transplants throughout Australia and New Zealand. According to the most recent publically available annual report, there were 60 patients in Australia and New Zealand who received ASCT for HL in 2014 (see Figure 2, below).[22] Data regarding the cause of death in the first 12 months post-transplant for the years 1998-2013 shows that of the patients who died within the first 12 months after ASCT, around 20% of patients being treated with ASCT died from complications related to ASCT and around 70% of deaths were due to progressive disease.

Figure 2. Primary cause of death in the first 12 months following ASCT in Australia 1998 to 2013

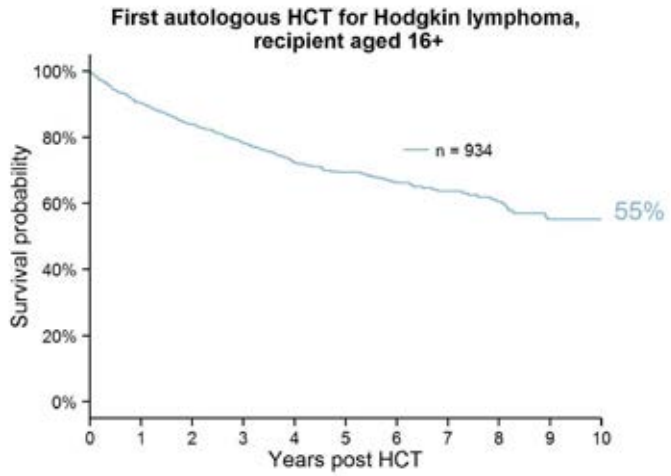


Cause of death	Recipient 0-15		Recipient 16+		Total	
Disease relapse or progression	160	87.0%	1,377	69.7%	1,537	71.2%
Transplant related	19	10.3%	419	21.2%	438	20.3%
New malignancy	0	0.0%	11	0.6%	11	0.5%
Unknown	5	2.7%	146	7.4%	151	7.0%
Other	0	0.0%	22	1.1%	22	1.0%
Total deaths	**184**	**100%**	**1,975**	**100%**	**2,159**	**100%**

The ABMTRS 2014 summary also provided 10 year survival curves according to condition requiring ASCT. The curve for HL is shown below in Figure 3.

Figure 3. 10 Year survival curve for patients aged 16+ years receiving ASCT for Hodgkin Lymphoma in Australia and New Zealand

[21] Australian Institute of Health and Welfare (AIHW) 2015. Australian Cancer Incidence and Mortality (ACIM) books: Hodgkin Lymphoma. Canberra: AIHW.
[22] Australasian Bone Marrow Transplant Recipient Society Annual Data Summary 2014.



This data indicates that around 45% of HL patients treated with ASCT in Australia develop progressive disease, and that this is a common cause of death in the first year after ASCT. The Australian patients who develop progressive disease following ASCT for CD30+ HL may be treated with brentuximab vedotin. This would indicate that the proposed indication for nivolumab would be applicable to only a very small number of Australian patients on an annual basis.

2.2. Clinical rationale

The Clinical Overview provides a Product Development Rationale. This includes a brief overview of Hodgkin lymphoma and of the treatments available for relapsed/refractory patients. The overview notes that '*The median OS of patients who relapse after ASCT was initially reported to be < 1 year; more recent data suggests that the median OS is evolving and may be closer to 2 years because of the availability of newer therapies like brentuximab'* and that *'the intended patient population for this submission are the heavily pretreated patients with cHL who have no other approved treatment options after failure of ASCT and brentuximab vedotin treatment, or at least 2 prior regimens in patients who are not ASCT candidates'.*

The following summary *'of the irregular and often limited efficacy of some of the various agents investigated prospectively for relapsed or refractory HL post ASCT'* was provided (shown in Table 6, below).

Table 6. Summary table of novel single agent therapy in cHL

Agent(s)	Pub Date	Target Population	No. Treated	Prior ASCT	ORR (%)	CR (%)	PFS	DOR	Overall Survival
Brentuximab vedotin[24]	2012	Relapsed Refractory after ASCT	102	102	75%	34%	6 Month PFS: ~45% 1 Year PFS: ~35%	6.7 months	6 Month OS: ~95% 1 Year OS:89%
Panobinostat[25]	2012	Relapsed Refractory after ASCT	129	129	27%	4%	6 Month PFS: ~ 60% 1 Year PFS: ~ 40%	6.7 months (median)	6 Month OS: ~90% 1 Year OS: 78%
Everolimus[26]	2010	Relapsed Refractory HL	19	16	47%	5%	6 Month PFS: ~ 50% 1 Year PFS: ~ 26%	7.1 months (median)	6 Month OS: ~85% 1 Year OS: ~75%
Bortezomib[27]	2006	Relapsed Refractory HL with 2 prior regimens including stem cell transplant	14	13	7%	0	NS	NS	NS
Gemcitabine[28]	2004	Relapsed of chemo-refractory HL; received ≥ 2 prior different chemo regimens	27	16	22%	0	1 Year PFS: 24%	NS	1 Year OS: 64% 2 Year OS: 55%
Rituximab[29]	2003	Recurrent cHL with minimum 2 prior treatment regimens	22	18	22%	5%	NS	7.8 months (median)	NS

Abbreviations: ASCT = autologous stem cell transplant; cHL = classical Hodgkin lymphoma; CR = complete response; DOR = duration of response; HL = Hodgkin lymphoma; NS = not stated; ORR = objective response rate; OS = overall survival; PFS = progression free survival.
Note: Approximate (~) indicates estimation from Kaplan-Meier curve.

Patients with cHL who progress after brentuximab and ASCT (or who are not candidates for ASCT) are described as having high unmet medical need due to *'no approved therapies, and the available treatment options have limited clinical activity and cause considerable toxicity*'. Brentuximab vedotin is briefly mentioned, together with its recognised adverse effect of peripheral neuropathy.

The nivolumab clinical development programme is briefly described, including the two studies supportive of efficacy for the proposed indication, with efficacy further supported by an integrated analysis of the results from the two studies. A similar approach was to be used for safety.

Comment: The Clinical Overview provides a limited discussion of treatment options available to patients with r/r cHL following ASCT ± brentuximab vedotin. The discussion does not include allo-SCT, RIC allo-SCT, combination chemotherapy or DXRT.

2.3. Guidance

The sponsor has presented interim results from an ongoing Phase II study and an ongoing Phase I study to support efficacy, with no apparent intention to conduct any Phase III confirmatory trial.

According the dossier, a 'pre-submission' meeting with the TGA was requested by the sponsor. The email in which this request was made noted that '*Efficacy data to support the proposed indication in cHL is based on integrated clinical data derived from 2 studies: CA209205 (Phase II) and CA209039 (Phase I)'* and that *'Following feedback from the EMA and FDA [the sponsor] has made the decision to file the integrated data from CA209205 (cohort B) and CA209039 as a first submission globally'*. The information that no Phase III study is planned was also provided with '*The available evidence for submission supports a very narrow indication for which it was not possible to recruit a sufficiently large number of patients to conduct a reasonably powered, randomised Phase III study. As a consequence [the sponsor] has not conducted nor is planning a confirmatory Phase III study in this precise patient population due to the small number of subjects available, the late stage of disease and the absence of an approved comparator.'* The sponsor's cover letter provides the following additional information: *'[the sponsor] is however planning a Phase III trial in an earlier treatment line in subjects with cHL. Study design options are still being investigated'.*

The meeting request was rejected by the TGA as the proposed timing of the requested meeting was after the sponsor had lodged the Pre-submission Planning Form. The following written advice was provided to the sponsor by email:

> *'The Delegates have had a brief discussion and noting [the sponsor] has already the lodged the PPF, and are aware that rolling data submissions are not permitted by the TGA, do not see that a teleconference in March will assist in evaluation of the lodged application. For clarification, the Delegates note that safety data can be accepted at any time, but additional efficacy data will only be accepted and will only be evaluated if requested by the TGA.*
>
> *These are standard rules and we do not see a 'post submission' teleconference will assist the TGA in understanding or evaluating what the sponsor has already been determined will be submitted. Once an application is lodged, the TGA has opportunities for clarification at the [consolidated request for further information from sponsor] and pre-ACPM response stages. The TGA's approach will be standard in considering whether quality, safety and efficacy have been established. Any reliance on early data where there are immature or surrogate endpoints would need to be communicated prominently and clearly in the PI, and for such applications, the TGA has been requiring a Note to the Indication and a statement in the Clinical Trials section.*
>
> *Consideration by the TGA will also be given to the need for a registry. These matters which would normally be discussed in a pre-submission meeting, are being communicated now for the sponsor's consideration in submitting the PI with the data in May.'*

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier contained the following:

- Interim Clinical Study Report for Study CA209205
- Interim Clinical Study Report for Study CA209039
- Integrated Summary of Safety. This includes safety data from all cohorts in the Studies CA209205 and CA209039. Comparison is made to nivolumab monotherapy safety data from solid organ tumours (renal cell carcinoma, melanoma, and non-small cell lung cancer)
- Population Pharmacokinetic and Exposure-Response Analysis of nivolumab in the treatment of subjects with cHL who have failed ASCT and brentuximab vedotin treatment
- Summary of Clinical Pharmacology; Summary of Clinical Efficacy dated (both dated February 2016); and a Clinical Overview of classical Hodgkin lymphoma.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

The sponsor's Clinical Overview states: '*All studies in the nivolumab cHL development program were conducted in accordance with the principles of GCP as defined by the ICH and were conducted to meet the ethical requirement of European Directive 2001/20/EC'.*

3.4. Evaluator's commentary on the clinical dossier

The assessment of efficacy and safety for this submission must be based on the interim results of 2 small early phase open label single arm studies using a surrogate endpoint. The sponsor has indicated that there is no intention to conduct a confirmatory Phase III study, although this does not appear consistent with the post market requirements for FDA approval. In this situation, a Note to the Indication that explicitly describes the quality of evidence on which the indication may be approved is essential (see Question 4: Note to the indication in Section 11, below).

Overlapping nivolumab submissions to the TGA have created some difficulties in the documentation for this submission. Each of the proposed documents provided with this submission includes information related to nivolumab use in advanced RCC. The submission for the RCC indication is currently under evaluation by the TGA and extensive changes to the PI were recommended by the evaluator and delegate for that submission. These changes are under negotiation between the TGA and sponsor. Later versions of both the EU RMP (Version 6.0) and ASA (Version 5.0) have also been provided to the TGA during the round 2 evaluation process for the RCC submission. Their inclusion in this cHL submission was requested by the sponsor on 1 July 2016. These documents include the proposed extensions of indications of cHL and SCC of the head and neck.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Only limited new pharmacokinetic data was provided in this submission, with this related to serum nivolumab measurements using a sparse sampling model for both Study CA209205 and Study CA209039.

Study CA209205 had an exploratory objective '*to characterize the pharmacokinetics (PK) of nivolumab and explore the exposure-response relationship*'. Study CA209039 had the secondary objective of '*To characterize the pharmacokinetics of nivolumab in subjects with relapsed/refractory hematologic malignancy*'. By-subject listings of serum nivolumab concentrations were provided in the interim CSRs but not further discussed or analysed. Instead, the results were '*combined with data from other studies in the clinical development program to develop or refine a population PK model and E-R analyses*'.

The following pharmacometric analyses of nivolumab in the treatment of patients with cHL who have failed ASCT and brentuximab vedotin treatment are provided in the submission: a PPK analysis, one Exposure-Response (E-R) efficacy analysis and one E-R safety analysis.

4.2. Summary of pharmacokinetics

The pharmacokinetics of nivolumab was evaluated in the CER for the first submission of nivolumab as a new chemical entity (NCE), Submission PM-2014-03852-1-4. According to the CER, *'There were only two studies in the submission in which intensive PK sampling was conducted. In study MDX-1106-01, intensive sampling was conducted after a single dose of nivolumab. In study MDX-1106-03 (CA209003) intensive sampling was conducted after single and multiple dosing. In the remainder of the studies in the submission, only sparse PK sampling was conducted and these data were analysed in population PK analyses. All the submitted studies were conducted in subjects with advanced cancer.'* In subsequent submissions, serum nivolumab concentrations have been collected using a sparse sampling model and used in population PK analyses. As a result, the description of nivolumab pharmacokinetics is largely dependent on PPK analyses.

The following description of nivolumab pharmacokinetics is based on the CERs for earlier submissions and the CHMP Assessment Report for Opdivo.[23] The results of the PK components of Studies CA209205 and CA209039 and the PPK analysis included in this submission are referred to where appropriate.

Nivolumab is a fully humanised IgG4 monoclonal antibody, produced in a Chinese hamster ovary (CHO) cell line. It contains two identical heavy chains of 440 amino acids each and two identical kappa light chains of 214 amino acids each. It has a molecular weight of 146 kDalton.

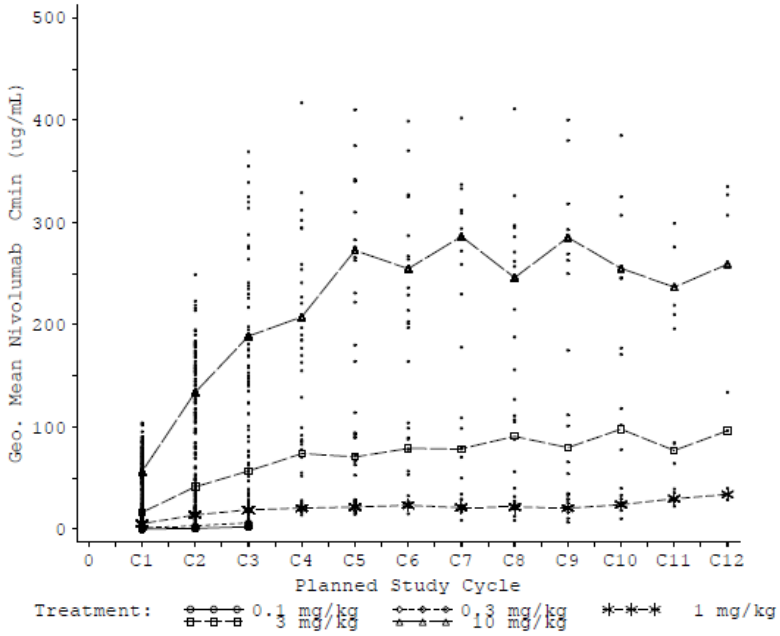
The dose proposed for nivolumab monotherapy is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Dose intervals of 3 weekly have also been used in nivolumab monotherapy studies in the clinical development programme.

Pharmacokinetics has mainly been documented in patients with different types of solid tumours (NSCLC, Melanoma, RCC, colorectal cancer, CRPC, others) and not in healthy volunteers.

Pharmacokinetics of nivolumab in these patients appeared dose proportional over the dose range 0.1 mg/kg to 10 mg/kg. No signs of time dependent PK parameters were observed over the period studied. The multiple-dose PK of nivolumab given 3 mg/kg every 2 weeks was mean clearance of 10.3 mL/hr and mean effective half-life of 27.5 days. The elimination and distribution of nivolumab appeared to be independent of the dose in the dose range studied and also independent of tumour type in the studied solid organ tumour types.

From the CSR for Study MDX1106-03, a dose escalation study in patients with advanced solid tumours, '*there was no dose-related trend in accumulation of C_{min}'.* Time to steady state was difficult to determine due to the variability in individual C_{min} results (see Figure 4, below). However, it was considered that an approximate steady state was reached by the Cycle 3 dose.

Figure 4. Study MDX1106-03 Individual and mean nivolumab C_{min} by study cycle



The inter-individual variability in PK parameters was considered to be modest with coefficients of variation being < 30% for C_{max} and AUC, after single or multiple dosing.

The distribution, metabolism and elimination of nivolumab has not been characterised. It is expected that these will resemble those of endogenous immunoglobulin. Immunoglobulin G is largely confined to the extracellular fluid and is cleared through receptor mediated endocytosis

[23] Committee for Medicinal Products for Human Use (CHMP) Assessment Report Opdivo; 23 April 2015. European Medicines Agency (EMA); London, United Kingdom.

or non-specific endocytosis followed by proteolytic degradation into small peptides and amino acids, with this occurring mainly in hepatic or reticuloendothelial cells. Renal elimination does not occur due to the large molecular weight of monoclonal antibodies. The volume of distribution described for nivolumab is consistent with that of endogenous IgG. The estimated terminal half-life for nivolumab ranged between 17 and 25 days and is also consistent with that of human immunoglobulin. The proposed dosing interval of 2 weeks is shorter than the observed terminal half-life.

4.2.1. Serum nivolumab concentrations in Studies CA209205 and CA209039

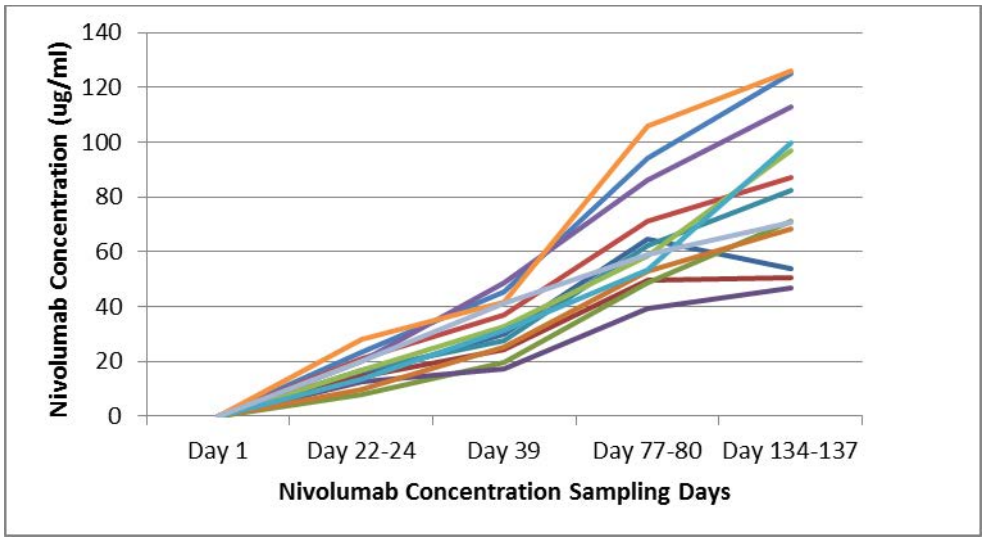
A by-subject listing of nivolumab concentrations was provided in an appendix to each of the interim CSRs. These were used to inform the sponsor's population PK analysis but not further analysed. The following analysis has been performed by the evaluator to illustrate some apparent differences in the handling of nivolumab by patients with cHL.

Comment: According to the sponsor's document Identification of errors of fact and/or material omission in the for Opdivo (Nivolumab) Clinical Evaluation Report Submission, the by-subject listing of nivolumab concentrations in the CSR appendices were only provided for subjects in whom there were also with ADA assessments and did not include all of the concentrations used in the PPK analysis and that these were provided in the appendices of the PPK analysis. This was further clarified in the response to a TGA Clinical Question which stated that [the appendix]: *'is not meant to represent an exhaustive list of PK samples, it is mainly a by-subject listing of nivolumab ADA with corresponding PK*'. According to the response to this question, there were, for example, 115 samples from Study CA209039 that did not have corresponding ADA assessments and were therefore not included in the appendix. This, unfortunately, was not readily apparent in the CSRs: the Pharmacokinetics Results section of each CSR provided a link to the appendix with the following wording, or similar, *'[the appendix] provides a by-subject listing of nivolumab concentrations along with corresponding immunogenicity*' (from the CSR for Study CA209039). As a result of this ambiguity in the CSRs the following analysis by the evaluator does not include all of the samples collected.

The reported serum nivolumab concentrations were identified by patient and study day and date: sampling that occurred during treatment versus follow-up visits was not identified as such in the source tables.

In Study CA209039, there were 23 patients with 1 to 8 serum nivolumab concentration results reported at scheduled time-points over a 1 to 12 month period. Many patients appeared to have missed one or more of the regularly scheduled time-points, with fewer than 15 patients having a sequence of 4 or more measurements, not including the baseline measurement. The reported concentrations ranged from the baseline concentration of < 0.2 μg/mL to 125 μg /mL. Individual subject nivolumab concentrations at scheduled time-points varied as much as 3 fold. There appeared to be a progressive increase in nivolumab concentration over time for those patients in whom consistent sampling in the first 4 to 6 months of the study occurred. Steady state did not appear to have occurred, even by Cycle 10 (approximate Study Day 140).

Figure 5. Serum nivolumab concentrations for individual patients over time in Study CA209039



Note: Each coloured line represents a single patient.

In Study CA209205, serum nivolumab concentrations were reported for patients from Cohort A, B and C (approximately 219 patients) with 1 to 4 results at scheduled time-points over a 1 to 6 month period. Due to missing results and staggered recruitment into each cohort, there were only 39 patients who had a sequence of 3 or more measurements at the scheduled timepoints, not including the baseline measurement. The reported concentrations for all patients ranged from < 0.2 µg /mL (baseline measurement) to 175 µg /mL, with considerable inter-patient variability. As with Study CA209039, in those patients with a sequence of 3 serum concentration measurements at regularly scheduled timepoints after Baseline, there appeared to be a progressive increase in nivolumab concentration over time.

Table 7. Nivolumab Concentrations for patients with a complete sequence of 3 samples after Baseline in Study CA209205

	Pre-dose Cycle 3	Pre-dose Cycle 7	Pre-dose Cycle 13
Median nivolumab concentration (µg/ml)	42.8	76.7	102
Minimum concentration (µg/mL)	25.6	46.8	60.2
Maximum concentration (µg/mL)	72.9	114	175

Of note in Studies CA209039 and CA209205 is the small number of patients who had completed sampling according to the pre-specified schedule. If baseline samples are not included, only 15 patients had a sequence of 4 post-baseline samples collected in CA209039 and only 39 patients had a sequence of 3 post-baseline samples collected.

Inter-individual variability is also notable in the by-subject listings. In Study CA209205, for patients who had a complete sequence of 4 specimens at Baseline, pre-dose Cycle 3, pre-dose Cycle 7 and pre-dose Cycle 13, inter-individual nivolumab concentrations at similar time-points could vary by 2 to 3-fold. Inter-individual variability in PK parameters has been described as 'modest' in patients with solid tumours. It is not clear to the evaluator as to whether inter-individual variability in serum nivolumab as seen in patients with cHL is consistent with that of patients with solid tumours (see Question 11: Inter-individual variability in serum nivolumab concentrations in Studies CA209039 and CA209205).

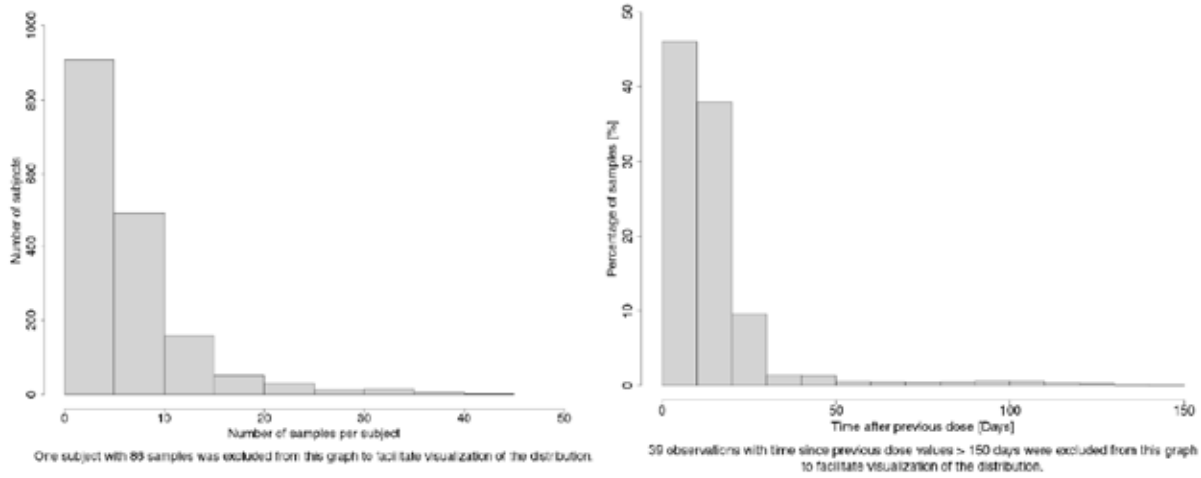
Comment: Of note, is that the analysis of the PK results for Study CA209039 provided in response to TGA questions, found that steady state was not reached until Week 20 (compared to Week 12 in patients with solid tumours) and that inter-individual variability (according to CV% of geometric means for C_{max} and AUC_{0-336}) was < 30% and consistent with that seen in patients with solid tumours.

4.2.2. Population pharmacokinetic study

A sequence of population pharmacokinetic studies has been included in the recent nivolumab submissions. Each analysis has been revised to include data from the target population for each submission, with comparison then made to reported measurements and other tumour types. The PK of nivolumab in patients with solid tumours was initially characterized by a PPK analysis with data from 6 clinical studies (3 Phase I and 3 Phase II studies). This initial PPK analysis has since been updated to include data from a Phase III study of subjects with advanced melanoma, data from 2 Phase III studies of subjects with NSCLC, and data from a Phase III study of subjects with RCC. These 9 studies included dose escalation studies, with doses ranging from 0.1 mg/kg to 10 mg/kg, and studies and varying dosing intervals (dosing interval every 3 weeks: Studies CA209010 and ONO-538-02; dosing interval every 2 weeks: Studies CA209003, CA209017, CA209057, CA209063, CA209025; first dosing interval 3 weeks and subsequent intervals 2 weeks: Study CA209005; dosing interval 4 weeks: Study CA209001).

A sparse sampling model of individual patients was used in almost all of these studies. The distribution of samples per patient and samples according to time since previous dose was provided in the most recent PPK analysis. The source table was not provided. Using the figures to estimate numbers, of the 1732 1677 patients (Round 2 comment: correction provided by the sponsor) included in the analysis, approximately 1400 had fewer than 10 serum samples collected; of the 11,392 sample results included, approximately 93% were collected within 25 days of the previous dose (that is, within one half-life).

Figure 6. Distribution of number of samples per patients and the number of samples according to time since dose



The population PK model developed using this data from patients with solid tumours was a linear, two-compartment, zero-order intravenous (IV) infusion model with first-order elimination. Comparison of predicted measurements to observed measurement was found to be less consistent for the timeframe 50 days to 300 days post-infusion. The report notes that no conclusions can be made for predictions beyond 300 days due to the '*very small number of samples associated with sampling times greater than 300 days post-infusion*'.

Using the model, nivolumab PK was described as dose independent, and time invariant. The geometric mean of terminal half-life (T-1/2β) was 26.2 days and the typical clearance (CL) was 8.15 mL/h. This was said to be consistent with the PK of full human IgG antibodies. Body weight is described as the most influential covariate on nivolumab PK: nivolumab CL and VC increased

with increase in baseline BW. The magnitude of this effect varies with tumour type (approximately 26% and 21% in NSCLC, 30% and 25% in RCC). Nivolumab CL also appeared to decrease with increasing serum albumin. Several other covariates had statistically significant effects on the CL of nivolumab (sex, ECOG status, baseline serum LDH, and eGFR). These are not considered to be clinically relevant by the sponsor as the magnitude of the effects was less than the '*20% boundary*'. Renal function, age, race, tumour type, baseline tumour burden and tumour volume, hepatic impairment status (by NCI Criteria), PD-L1 expression, and immunogenicity (ADA status) were not considered clinically relevant predictors of nivolumab CL in subjects with advanced melanoma. Of note, however, is that children, patients with severe renal or moderate or severe hepatic impairment and patients with ECOG status > 1 have been excluded from the clinical studies.

Comment: The magnitude of the effect of body weight varying with tumour type was identified as an error by the sponsor's document: Identification of errors of fact and/or material omission in the for Opdivo (Nivolumab) Clinical Evaluation Report Submission. The statement provided regarding this in the CER is taken directly from the Introduction section of the PPK analysis. This is made clear in the summary of the PPK analysis provided [not included here]. The sponsor wished to replace the statement regarding variation with tumour type by: '*Compared to median body weight (76.3 kg), the magnitude of this effect varies with extremes of body weight. (approximately 31% and 25% increase in subjects with 95 percentile body weight (116.7 kg), 29% and 24% decrease in subjects with 5 percentile body weight (50 kg)'.*

For the PPK analysis provided with the current submission, data from Studies CA209039 and CA209205 were used to further characterise the PK of nivolumab in subjects with cHL. The PPK analysis included all 23 subjects from Study CA209039. According the PPK report, there were 224 samples from Study CA209039 included, an average of 9 samples per patient. Of note is that the first dosing interval in Study CA209039 was 3 weeks, with subsequent doses administered every 2 weeks. All subjects for whom serum samples were available from each of the 3 cohorts in Study CA209205 were to be included in the PPK analysis. However, of the 239 patients who had been treated with nivolumab at the time of the analysis, only 170 patients were included. There were 36 patients excluded due to having pre-treatment specimens only. The reason(s) for not including the other 33 patients was not provided. There were 344 samples included from Study CA209205, an average of 2 samples per patient. The dosing interval in this study was every 2 weeks.

Comment: There are a number of uncertainties related to the data from Studies CA209039 and CA209205:

1. The number of samples from Study CA209039:

   According to a table in the PPK report, there were 224 samples from Study CA209039 included. This is not consistent with the information in an appendix of the CSR for Study CA209039 that *'provides a by-subject listing of nivolumab concentrations along with corresponding immunogenicity*'. This appendix has only 99 serum nivolumab results (not including baseline samples) (see Question 7: The PPK analysis and the number of samples from Study CA209039 in Section 11, below).

2. The number of patients from Study CA209205:

   According to a table in the PPK report, there were 239 patients who had been treated with nivolumab at the time of the analysis. Of these patients, 170 were included in the analysis with 36 not included due to having pre-treatment specimens only. The reason(s) for not including the other 33 patients were not provided (see Question 6: The PPK analysis and number of patients from Study CA209205 in Section 11, below).

3. The number of patients with sequential sampling included in the analysis:

According to the number of samples and patients, there was an average of only 2 samples per patient for Study CA209205. It is not clear as to the average number of samples per patient for Study CA209039. From the by-subject listings provided in the Study CA209039 only 15 patients had regular nivolumab concentrations reported for time-points during the first 4 to 6 months; in Study CA209205 only 39 patients had a sequence of 4 serum concentration measurements available. For the PPK analysis to be meaningful and reliable, sequential sampling of a reasonable number of patients is necessary (see Question 8: The PPK analysis and sample distribution for Studies CA209039 and CA209205 in Section 11, below).

The discrepancies in the number of samples described in the tables in the PPK analysis and in the appendix of the CSRs have been explained by the sponsor and have been described above.

Model development followed the same process as that for previous PPK models in the sequence, with testing of the same co-variate effects on nivolumab clearance.

The previously developed model was described as showing good fit with the inclusion of data from patients with cHL. However, it was noted that the model was less consistent for the timeframe 50 days to 300 days post-infusion, with this attributed to the small number of samples during this period.

As in previous PPK analyses, the final model was a 2-compartment model with zero-order IV infusion input and first-order elimination. As previously, body weight and albumin were found to have the greatest effect on clearance, although this was considered clinically relevant for body weight only. Nivolumab clearance was found to be approximately 13% greater in the presence of nivolumab ADA, as compared to subjects with negative ADA assay values. However, this effect was not considered clinically meaningful because the '*magnitude was modest, ADA was time varying, and the effects of ADA only occur for a fraction of the treatment period*'.

Comment: according to the interim CSRs, only one patient in each study tested positive to ADA whilst on treatment. Any conclusions regarding the effect of positive ADA status on nivolumab clearance in patients with cHL should be interpreted cautiously.

The PK parameters of clearance and half-life for subjects with cHL differed from those of subjects with solid tumours, resulting in a difference in nivolumab exposure. According to the PPK study report this was the first instance of different CL by tumour type observed in the nivolumab development program.

Table 8. Summary statistics for PK parameters and exposure for patients with solid tumours or with cHL

PK Parameter or Exposure	Subjects with solid tumours		Subjects with cHL	
	Median	min, max	Median	min, max
Clearance (CL) (L/h)	0.00912	0.00138, 0.0436	0.0057	0.00292, 0.024
Volume of Distribution (L)	7.74	2.5, 27.1	7.6	4.72, 17.2
Terminal half-life (days)	26.1	5.78, 554	40.6	11.5, 64.4
Cavg1	26.9	8.03, 72.4	28.2	4.9, 45.2
Cmin,ss	59.5	7.43, 375	98.8	25, 186

PK Parameter or Exposure	Subjects with solid tumours		Subjects with cHL	
	Median	min, max	Median	min, max
Cmax,ss	120	48.5, 1270	152	40.7, 246
Cavg,ss	77.7	18.9, 394	116	29.6, 206

This decrease in CL resulted in approximately 43% increase in average exposure ($C_{avg,ss}$) in cHL subjects relative to solid tumour subjects.

In the Summary of Clinical Pharmacology, the sponsor comments that '*a difference in the CL of monoclonal antibodies across different disease states has been reported previously*'.[24] The cited reference to this comment describes higher clearance of rituximab in patients with NHL compared to patients with CLL and suggests that a higher dose of rituximab may be required in patients with CLL.

The increase in nivolumab exposure in patients with cHL was assessed by the sponsor as not being clinically meaningful, '*as the E-R safety analysis demonstrated that exposure was not a predictor of the risk of G3+ DR-AEs, and the safety profile following administration of nivolumab to subjects with cHL was similar to that observed in other tumor types and no new safety findings were found in cHL population.'* As a consequence, there was no discussion of dose reduction or dose interval increase in this patient population.

Comment: The sponsor is asked to account for this difference in clearance and corresponding increase in exposure, in subjects with cHL and to provide an assessment of the implications for the dosing interval and/or dose in this patient group. The evaluator notes that the cited reference in the Summary of Clinical Pharmacology (Li et al) suggests that different doses of rituximab may be appropriate in different patient populations due to the differing clearance (see Question 10: Reduced clearance and drug accumulation in Studies CA209039 and CA209205 in Section 11, below). The evaluator also notes that this apparent difference in clearance of nivolumab by patients with cHL may be a product of the limited number of patients, limited sampling and inter-patient variability: in Study CA209039 only 14 patients had nivolumab concentrations reported for all scheduled time-points during the first 4-6 months (not including baseline); in Study CA209205 only 39 patients had a sequence of 4 serum concentration measurements available (including baseline); very few patients had any sampling more than 25 days post dose (see Question 9: Reliability of the PPK finding of reduced clearance and drug accumulation in Studies CA209039 and CA209205).

A new PPK analysis, using a time-varying clearance model, was provided with the sponsor's response to a clinical question (see Question 9: Reliability of the PPK finding of reduced clearance and drug accumulation in Studies CA209039 and CA209205 in Section 11, below). This new PPK confirmed also found that nivolumab has reduced clearance in patients with cHL compared to patients with solid tumours and further found that nivolumab had increased clearance in patients with gastric cancer. The evaluator does not find this variation in PK with different tumour types to be biologically plausible with the current understanding of nivolumab PK (presumed similar to those of endogenous immunoglobulins). It may be that this understanding is incorrect or that an appropriate PK model for nivolumab has yet to be determined.

[24] Li et al. Population pharmacokinetics of rituximab in patients with chronic lymphocytic leukaemia. J Clin Pharmacol 2012;52:1918-26. (Provided by the sponsor).

4.2.3. Pharmacokinetics in special populations

The following has been summarised from previous CERs for nivolumab submissions and the CHMP report. There is no new information provided in the current submission.

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

Nivolumab has not been studied in patients with moderate or severe hepatic impairment. PPK analysis found that subjects with mild hepatic impairment had similar CL and exposures relative to normal subjects, suggesting that no dose adjustment is needed for subjects with mild hepatic impairment. No subjects with moderate and severe hepatic impairment were included in the dataset for the PPK analysis. Therefore, no conclusions regarding the effect of moderate or severe hepatic impairment can be drawn.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

Specific PK studies in patients with renal impairment have not been conducted and patients with severe renal impairment (Cr > 1.5 x ULN or Cr Cl < 40 mL/min) were excluded from the efficacy studies. PPK analysis has shown a lack of effect on the PK of nivolumab in patients with renal impairment suggesting that no dose adjustment is needed for subject with mild and moderate renal impairment. However, no subjects with severe renal impairment were included in the dataset for the PPK analysis. Therefore, no conclusions regarding the effect of severe renal impairment can be drawn.

4.2.3.3. Pharmacokinetics according to age

Paediatrics

Children and adolescents (age < 18 years) have not been included in the Clinical Development Programme for nivolumab as provided to the TGA.

Elderly

There was no upper age limit in the efficacy studies and patients aged more than 85 years have been included in the clinical trials programme. In the CHMP Assessment Report for Nivolumab, a total of 369 patients aged 65 years or more and 117 patients aged more than 75 years had been included in the clinical trials programme.[23] The PPK analysis found that age did not affect nivolumab PK.

4.2.3.4. Pharmacokinetics according to other population characteristics

In the population PK analysis, bodyweight was found to have a significant effect on nivolumab PK. However, when administered on a dose per weight basis, nivolumab systemic exposure was considered to be comparable across a wide range of bodyweights. There were, however, very few patients at the extremes of body weight (< 40 kg and > 150 kg) included in the clinical development programme. Gender and race was assessed as not having a clinically significant effect on nivolumab PK. Patients in the clinical development programme were predominately Caucasian, with very few patients of Asian background.

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

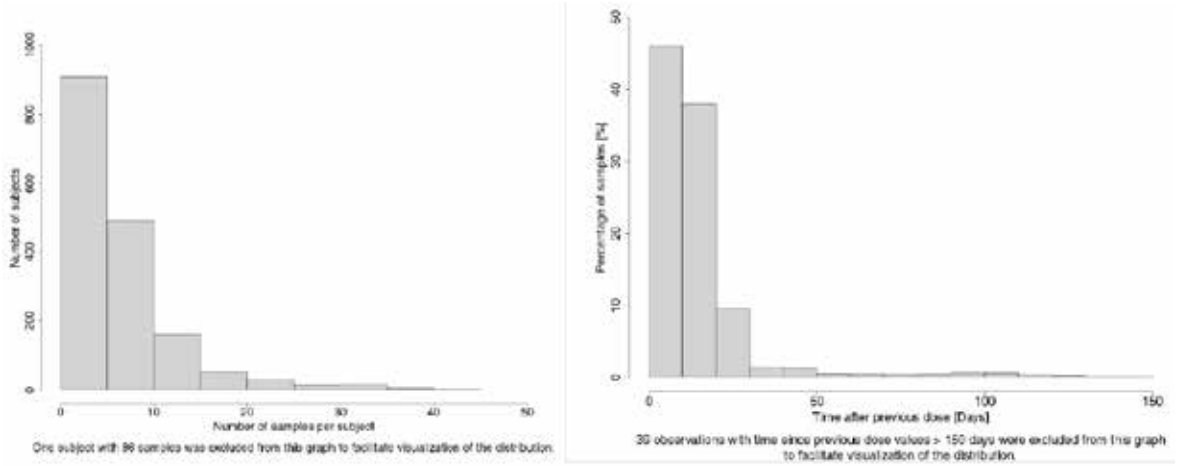
From the CHMP Assessment Report for Nivolumab: '*As nivolumab is not subject of metabolism by CYP450 enzymes no classical studies regarding metabolism or elimination were deemed necessary*'.[23] A dose escalation study in patients with advanced renal cell carcinoma was also referred to as showing no meaningful change in cytokine levels across all dose levels of nivolumab. The conclusion drawn in the CHMP report was that '*This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction'.*

4.3. Evaluator's overall conclusions on pharmacokinetics

There appears to have been limited investigation of the pharmacokinetics of nivolumab during the sponsor's clinical development programme. There has been no investigation of distribution, metabolism and elimination of nivolumab, with the assumption made that these would resemble the distribution, metabolism and elimination of endogenous immunoglobulin. This assumption has not been substantiated. Specific investigations of special populations have not been performed. In particular, patients with severe renal failure or hepatic failure or ECOG performance status > 1 have been excluded from the clinical studies.

Pharmacokinetic studies in the clinical development programme have largely consisted of sparse sampling of serum nivolumab concentrations, with these results used in a sequence of population PK analyses. Use of the sparse sampling model and dependence on PPK modelling is demonstrated in the following figures from the most recent PPK analysis: of the 1732 patients included in the analysis, only around 300 patients had more than 10 serum samples collected; of the 11,392 sample results included, approximately 93% were collected within 25 days of the previous dose (that is, within one half-life).

Figure 7. Distribution of number of samples per patients and the number of samples according to time since dose



According to the sponsor's documents, the population PK analyses have found that the PK variables predicted by the model were consistent with observed measures across solid tumour types and that inter-patient variability was 'modest'. The limiting factors of infrequent sampling and sampling confined to a relatively short period have not been discussed by the sponsor.

Patients with cHL appear to handle nivolumab differently from patients with solid tumours, although this analysis appears to be based on a small number of samples from a small number of patients. The previously developed PPK model was described as showing good fit with the inclusion of data from patients with cHL, although less consistent for the timeframe 50 days to 300 days post-infusion (with this attributed to the small number of samples during this period). However, the population PK analysis found that nivolumab clearance is reduced by one third in this population, with this, in turn, causing a 15 day increase in the half-life and a 43% increase in exposure (as measured by median $C_{avg,ss}$).

Table 9. PK parameters, comparison of subjects with solid tumours and subjects with cHL

PK Parameter or Exposure	Subjects with solid tumours		Subjects with cHL	
	Median	min, max	Median	min, max
Clearance (CL) (L/h)	0.00912	0.00138, 0.0436	0.0057	0.00292, 0.024

PK Parameter or Exposure	Subjects with solid tumours		Subjects with cHL	
	Median	min, max	Median	min, max
Terminal half-life (days)	26.1	5.78, 554	40.6	11.5, 64.4
$C_{avg,ss}$	77.7	18.9, 394	116	29.6, 206

The by-subject listings of nivolumab concentrations provided for the two studies in patients with cHL show both considerable inter-patient variability and progressive drug accumulation over time, with no apparent steady state reached. This should be interpreted with caution due to the number of missing scheduled samples and the small number of patients.

The different handling of nivolumab by this population and the implications of this on dose and/or dose interval have not been explored by the sponsor. The comment is made that '*a difference in the CL of monoclonal antibodies across different disease states has been reported previously*'. The cited reference to this comment (Li et al) describes higher clearance of rituximab in patients with NHL compared to patients with CLL and suggests that a higher dose of rituximab may be required in patients with CLL.[24] The increase in nivolumab exposure in patients with cHL was assessed by the sponsor as not being clinically meaningful, '*as the E-R safety analysis demonstrated that exposure was not a predictor of the risk of G3+ DR-AEs, and the safety profile following administration of nivolumab to subjects with cHL was similar to that observed in other tumor types and no new safety findings were found in cHL population.'* The evaluator does not find this argument convincing, given the relatively small number of subjects included in the two studies and their relatively brief periods of treatment and follow-up. The evaluator is also unsure as to whether there is a true difference in the handling of nivolumab by patients with cHL, again given the small numbers of patients and the limited sampling performed.

The results of the PPK analysis for patients with cHL has raised some larger questions: whether the pharmacokinetics of nivolumab have been adequately described by the PPK model; whether dependence on a sparse sampling process and PPK analysis is appropriate in early studies involving small numbers of patients; whether exposure related toxicities can be adequately assessed in small numbers of patients with limited follow-up.

The sponsor has proposed one change to the 'Pharmacokinetics' section of the PI. This change is to include the sentence '*Nivolumab CL in cHL patients was approximately 32% lower relative to NSCLC. This decrease in CL was not clinically meaningful'* in the 'Special Populations' section (draft PI version 2.2). This suggests a greater degree of certainty than is consistent with the information presented by the sponsor and does not explicitly state that this decrease in clearance was associated with an increase in exposure. It is also concerning to the evaluator that this information regarding a target population is placed in 'Special Populations'. The evaluator is of the opinion that more extensive changes to the 'Pharmacokinetics' section of the PI may be required. These would include an explicit statement that the pharmacokinetic measures quoted in the first paragraph refer to patients with solid tumours and a second statement regarding patients with cHL. Further revision may be required following evaluation of the sponsor's responses to clinical questions related to PK in patients with cHL.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Both Study CA209039 and Study CA209205 provided limited new pharmacodynamic data. These studies are described in Section 7: Clinical efficacy.

An exposure-response efficacy analysis and exposure-response safety analysis in patients with cHL were included in the pharmacometric report provided in the submission.

Table 10. Studies providing pharmacodynamic data

Study Identifier	Sub-topics
CA209039	Biomarker assessment (PD-L1 expression, 9p24.1 chromosomal abnormality, EBV status)
CA209205	Biomarker assessment (PD-L1 expression, 9p24.1 chromosomal abnormality)

The following table lists pharmacodynamic results that were excluded from consideration due to study deficiencies.

Table 11. Pharmacodynamic results excluded from consideration

Study ID	Subtopic(s)	PD results excluded
CA209039	PD-L1 status, 9p24.1 chromosomal abnormalities, pSTAT3 and EBV status	Efficacy analysis for each of these biomarkers

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

No description of the postulated mechanism of action for nivolumab is provided in the sponsor's Clinical Overview or Summary of Clinical Pharmacology. The following description is provided in the proposed PI:

> *'Pharmacology*
>
> *Mechanism of action*
>
> *Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb) which binds to programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses through blockade of PD1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.*
>
> *Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor responses in metastatic melanoma. In murine syngeneic tumor models dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumor activity.'*

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Elements of the mechanism of action were to be investigated in both Study CA209205 and Study CA209039.

Exploratory endpoints in Study CA209205 included:

- To investigate the association between biomarkers in the peripheral blood and tumour tissue, such as programmed death ligand 1 (PD-L1) expression, and safety and efficacy measures
- To evaluate the pharmacodynamic activity of nivolumab monotherapy in the peripheral blood and tumour tissue as measured by flow cytometry, immunohistochemistry (IHC), soluble factor analysis, and gene expression (microarray technology, quantitative reverse transcription polymerase chain reaction (RT-PCR).

Secondary and exploratory end-points in Study CA209039 included:

- To characterise the immunogenicity of nivolumab in subjects with relapsed/refractory haematologic malignancy
- To assess the potential association between anti-programmed-death 1 (PD-L1) expression on tumour cells as measured by immunohistochemistry and clinical efficacy measures
- To investigate the pharmacodynamic effects of nivolumab on selected markers of immune modulation in peripheral blood and tumour samples
- To investigate the potential association between selected biomarker measures and clinical efficacy measures.

Only a few of the pharmacodynamic results were provided in the interim CSRs:

- Study CA209205 reported the results of efficacy analyses according PD-L1 expression on RS cells and 9p24.1 chromosomal abnormalities.
- Study CA209039 reported the results of efficacy analyses according PD-L1 expression on RS cells and 9p24.1 chromosomal abnormalities (polysomy, gain, or amplification); PD-L1 and PD-L2 status by 'DFCI assay', pSTAT3 status by 'DFCI assay' and EBV status.

Both Study CA209039 and Study CA209205 used a different definition of PD-L1 expression compared to that used in solid tumours. In the cHL studies, PD-L1 expression was estimated according to the expression on R-S cells, but with no lower limit on the number of R-S cells per field. In general, R-S cells comprise 0.1 to 10% of the tumour bulk in cHL. Using this definition and ≥ 1% cut off, and given that R-S cells usually make up less than 1% of the tumour bulk, any patient with one R-S cell that expressed PD-L1 would be PD-L1 positive, even if there was only one R-S cell on the slide. In solid tumours, PD-L1 expression was estimated according to the expression on tumour cells, with a minimum of 100 assessable tumour cells per slide. Due to the use of differing definitions of PD-L1 expression, no comparison of the results for PD-L1 expression in patients with cHL can be made to the results in patients with solid tumours.

Both studies found high PD-L1 expression in those patients for whom there were PD-L1 quantifiable specimens. Both studies also found that all patients for whom there were 9p24.1 quantifiable specimens, had at least one 9p24.1 chromosomal abnormality (polysomy and/or copy number gain and/or amplification). This suggests that R-S cells commonly express P-L1 and that 9p24.1 chromosomal abnormalities are common in cHL. These findings should, however, be interpreted with care due to the high proportion of missing results.

Study CA209205 found no significant difference in outcome (ORR by IRRC) between PD-L1 positive and PD-L1 negative patients. However, this result should be interpreted with care due to missing results (PD-L1 quantifiable specimens were available for only 63/80 patients) and to the small numbers of PD-L1 negative patients (6/63) to act as comparators. The analysis of

efficacy according to 9p24.1 chromosomal abnormalities found that 45 patients had quantifiable specimens available, all 45 had an abnormality of 9p24.1 and that the ORR by IRRC was similar across the three groupings of abnormalities. Interpretation of this is difficult given that many patients had more than one abnormality type.

For Study CA209039, no conclusions can be drawn from the reported results due to the high proportion of missing results: only 10/23 patients had evaluable or quantifiable specimens for PD-L1 expression and 9p24.1 chromosomal abnormalities.

5.2.2.2. Secondary pharmacodynamic effects

No investigations of secondary pharmacodynamics effects were presented or described, although immune-mediated adverse reactions may be considered a secondary pharmacodynamics effect. These are discussed in the section on clinical safety below.

5.2.3. Time course of pharmacodynamic effects

5.2.3.1. Tumour response

Some information regarding the time course for the pharmacodynamics effect of tumour shrinkage is available in the results of the two studies. Unlike conventional chemotherapy drugs that may result in a decrease in tumour size over weeks, immune checkpoint inhibitors can take several months to have this effect. This is confirmed in both studies.

In Study CA209205, tumour response was assessed by IRRC according to the 2007 International Working Group (IWG) criteria and regularly scheduled CT scans, starting at Week 9. There were 80 patients enrolled in Cohort B of the study and the median duration of follow-up for these patients was 8.9 months (range 1.9, 11.7). Of the 80 patients, 53 had a best overall response (BOR) of complete response (CR) or partial response (PR). For these patients, the time course of tumour response was:

- The median time to response (TTR) was 2.1 months (range 1.6 months to 5.7 months)
  - 31 of the 53 (58.5%) responders achieved their response by the time of first scan (9 weeks), and all of the responses were achieved within 6 months of treatment initiation.
- The median time to CR was 4.44 months (range 3.3 months to 6.9 months)
- The median time to PR was 2.10 months (range 1.6 months to 5.7 months)
- The median duration of response per IRRC 7.8 months (95% CI 6.64, NA).

In Study CA209039, tumour response was assessed prospectively by investigators (and retrospectively by IRRC). In 11/20 responders per investigator the BOR response occurred within 9 weeks of commencing treatment. However, in some patients, BOR was not achieved for 6 months or longer. Durable responses were achieved in some patients. At the time of DBL, in 3 patients with BOR of CR or PR by IRRC, the response had been present for more than 12 months. The range of duration of response was 1.8 to 23 months.

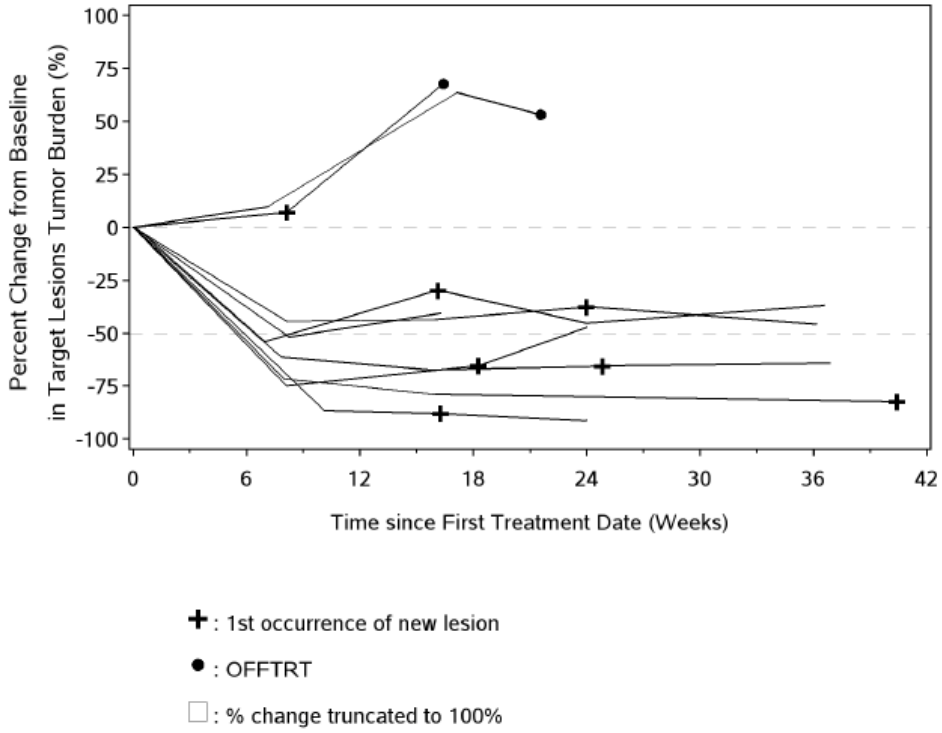
5.2.3.2. Pseudoprogression

It is thought that immune checkpoint inhibitors may cause an initial increase in tumour size ('pseudoprogression'), with this presumed due to infiltration of the tumour by immune system cells and the associated inflammatory effect, rather than being due to tumour progression. This initial increase in size may be followed by shrinking or eradication of the tumour. Both Study CA209205 and Study CA209039 allowed patients with progression according to the IWG criteria to be continued on treatment at the discretion of the investigator.

During Study CA 290205, there were 23 patients who had progressed, according to the 2007 IWG criteria as assessed by the investigators. Of these patients, 9 patients were considered eligible per protocol to receive continued nivolumab therapy. The number of doses received beyond progression ranged from 1 to 14 and the duration of treatment beyond progression ranged from 0.5 to 6.4+ months. Among these 9 subjects treated beyond progression, 6

maintained tumour reduction in target lesion. Of these 6 subjects, 5 maintained reduced tumour burden after the appearance of new lesions and the other had a new lesion at the data cut-off.

Figure 8. Plot of tumour burden change over time in Cohort B patients 'treated beyond progression



Response Evaluable: Subjects with i) a BOR of CR, PR, SD or PD, ii) target lesion(s) assessed at baseline, and iii) at least one on-study timepoint with all baseline target lesion(s) assessed.
Horizontal reference line indicates the 50% reduction consistent with a response per revised 2007 IWG criteria.
Assessments are per Investigator using 2007 IWG criteria.
Subjects treated beyond progression are defined as subjects whose last available dose date is after the date of initial progression per 2007 IWG based on investigator assessment.

Note: IWG definition of PR requires ≥ 50% decrease in sum of the product diameters of target lesions.

In Study CA209039, there were 4/23 patients treated beyond disease progression. According to the definition of BOR per investigator, 3 of these subjects were subsequently classified as responders:

- In the ASCT-Bren Failed group:
  - One patient achieved PR followed by disease progression. Disease progression persisted despite continuation of treatment
  - One patient had initial disease progression followed by PR with ongoing study drug treatment with disease progression then occurring after approximately 12 months of treatment.
- In the Other cHL group
  - One patient had an 'unconventional response' with increase in tumour burden initially and then PR with study drug continuation. The patient subsequently discontinued treatment and underwent allo-SCT
  - One patient had initial disease progression. With continued study drug treatment, there was a reduction in tumour burden but not sufficient to reach PR. Disease progression subsequently occurred.

It is not clear in the CSR of either study as to how patients who were treated beyond progression were chosen from the group of patients who progressed (see Question 22: Treatment beyond progression in Study CA209205 and Question 23: Treatment beyond progression in Study CA209039 in Section 11, below).

5.2.4. Relationship between drug exposure and pharmacodynamic effects

The submission included two Exposure-Response analyses of nivolumab: an Exposure-Response efficacy analysis and an Exposure-Response safety analysis. In both analyses, the exposure was determined by the $C_{avg,ss}$, with this, in turn, calculated from the PK simulation.

Of note is that:

- the analyses include different populations of subjects: the PPK study and the E-R Safety analysis both include all 23 subjects from Study CA209039 and 170 subjects from Study CA209205 (from Cohorts A, B and C); the E-R efficacy analysis includes 15 subjects from Study CA209039 and 77 patients from Cohort B in Study CA209205 (patients with cHL who had failed both ASCT and brentuximab vedotin).
- due to staggered recruitment, the duration of follow-up for the three cohorts in Study CA209205 differed considerably with median duration of follow-up of 5.1 months for Cohort A, 8.9 months for Cohort B and 2.8 months for Cohort C.

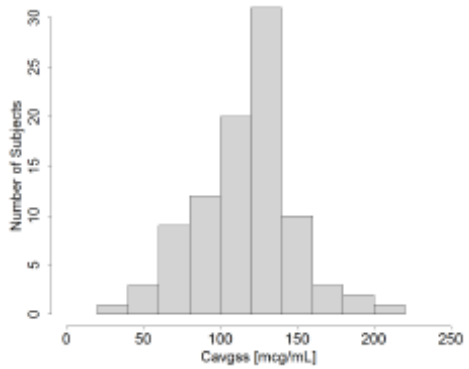
5.2.4.1. Exposure-Response efficacy analysis

The exposure-response efficacy analysis had the objective of characterising the relationship between nivolumab exposure and efficacy in subjects with cHL who have failed ASCT and brentuximab vedotin treatment and were treated with nivolumab, as measured by IRRC assessed ORR.

The analysis included 15/23 subjects in the cHL cohort of CA209039 (8 were excluded as these patients had not failed both ASCT and brentuximab vedotin) and 77/80 subjects from Cohort B of Study CA209205 (3 subjects were excluded due to unavailability of nivolumab exposure estimates).

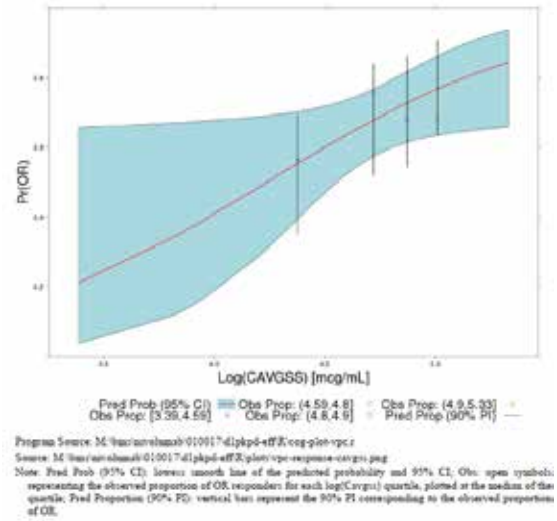
The following distribution of exposure ($C_{avg,ss}$) in the subjects included in the analysis was provided, shown below in Figure 9.

Figure 9. Distributions of exposure in the E-R efficacy analysis dataset



According to the analysis, Log-transformed $C_{avg,ss}$ was found to be a significant predictor of Pr(OR), for IRRC assessed OR. The exposure-response curve is shown below in Figure 10.

Figure 10. Exposure-response curve for IRRC assessed objective response



The 95% CI of all other predictor variables evaluated (sex, age, BW, ECOG status, and number of prior therapies) included unity, indicating a lack of evidence for the effect of these variables on Pr(OR).

The final model from IRRC-assessed objective response was used to predict Pr(OR) at the median and 5th/95th percentiles of $C_{avg,ss}$. The Pr(OR) was predicted to be approximately 36% lower for a subject with $C_{avg,ss}$ at the 5th percentile (67.03 µg/mL) compared to a subject with the median $C_{avg,ss}$ (148.4 µg/mL). However, there was minimal difference (3%) for a subject with $C_{avg,ss}$ at the 95th percentile (161.9 µg/mL) compared to a subject at the median $C_{avg,ss}$, suggesting a flat range in the exposure-response curve at higher concentrations.

Table 12. Model predicted probability of OR (Pr(OR)), by $C_{avg,ss}$ percentiles

Cavgss (mcg/mL)	Pr(OR)	95% CI of Pr(OR)
Median (148.4)	0.767	0.430 - 0.935
5th Percentile (67.03)	0.488	0.180 - 0.806
95th Percentile (161.9)	0.790	0.463 - 0.942

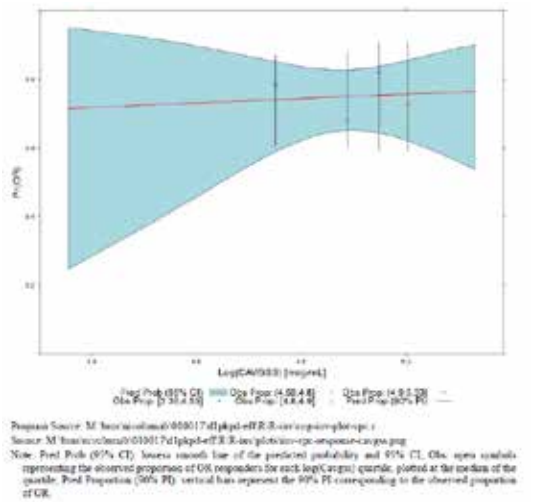
The following sensitivity analyses were performed using the full model and available data from Studies CA209039 and CA209205:

- The effect of 9p24.1 status on IRRC-assessed OR
- The effect of PD-L1 Status (1% cut-off) on IRRC-assessed OR. PD-L1 Status was not available in the analysis dataset for approximately 26% of subjects
- Investigator-assessed OR.

The report noted that 9p24.1 status was unavailable for approximately 19% of cHL patients and PD-L1 status for approximately 26% of patients. The sensitivity analyses with 9p24.1 or PD-L1 found that neither 9p24.1 nor PDL1 was a significant predictor of Pr(OR). Including the effect of 9p24.1 status or PD-L1 status in the full model resulted in ECOG status becoming a significant predictor of OR, but no other changes.

The investigator-assessed OR sensitivity analysis found that, unlike the main analysis, log-transformed $C_{avg,ss}$ was not a significant predictor of Pr(OR) in the full model. However, the estimated covariate effects were reported to be similar to the main analysis.

Figure 11. Exposure-response curve for IRRC assessed objective response



The report also noted that due to the decreased CL, the average nivolumab exposure in cHL subjects was increased by approximately 43% relative to solid tumour subjects. This increased exposure was not considered clinically relevant in cHL population, as at higher exposures, the Pr(OR) was in the '*flat range of the E-R curve*' regardless of the assessment modalities.

The report expressed concern that the relationship between efficacy and exposure may be unreliable '*due to the limited range of exposures in the analysis data, as all subjects were assigned the same nivolumab dosing regimen of 3 mg/kg Q2W and the sensitivity analysis indicated that only a few subjects were influential in explaining the discrepancy between the E-R results with IRRC- and investigator-assessed OR'.*

5.2.4.2. Exposure-response safety analysis

This analysis had the objective of characterising the relationship between nivolumab exposure and safety in subjects with cHL treated with nivolumab, as measured by Grade 3+ DR-AEs.

The E-R analyses of Grade 3+ DR-AEs included all 23 subjects from the cHL cohort of Study CA209039. Unlike the E-R efficacy analysis, subjects from all three cohorts of Study CA209205 could be included, provided the subject had received nivolumab treatment and for whom estimates of $C_{avg,ss}$ were available from the PPK analysis. In Study CA209205, 170 out of the 240 nivolumab-treated subjects were included. There were 70 subjects excluded (29.2%) (Cohort A: n = 16; Cohort B: n = 3; Cohort C: n = 51) as no nivolumab concentrations were available from these subjects after initiation of treatment.

Table 13. Summary of Grade 3+ DR-AEs in E-R safety analysis dataset

Study	Number of Subjects		
	Included in Analysis	Number With Events (%)	Number Censored (%)
CA209039	23	5 (21.74)	18 (78.26)
CA209205	170	29 (17.06)	141 (82.94)
Total	193	34 (17.62)	159 (82.38)

Comment: Recruitment into the cohorts of Study CA209205 was staggered, with patients recruited into cohort C after recruitment in Cohort B was complete. As a result the exposure to nivolumab was considerably lower in Cohort C, with the most of these patients having received three months of treatment at the time of the interim analysis, compared to 8 months for cohort B and 6 months for Cohort A. The following information (see Table 14, below) regarding the number treated in each cohort and nivolumab exposure is provided in the interim CSR for Study CA209205.

Table 14. Treated patients per cohort in Study CA209205 (Cumulative dose and relative dose intensity)

	Cohort A N = 63	Cohort B N = 80	Cohort C N = 97	Cohort A+B+C N = 240
NUMBER OF DOSES RECEIVED				
MEAN (SD)	11.1 (5.97)	16.1 (5.82)	6.4 (3.66)	10.9 (6.57)
MEDIAN (MIN - MAX)	11.0 (1 - 24)	17.0 (3 - 25)	6.0 (1 - 14)	10.0 (1 - 25)
CUMULATIVE DOSE (MG/KG)				
MEAN (SD)	32.84 (17.601)	47.91 (17.295)	18.97 (10.785)	32.26 (19.487)
MEDIAN (MIN - MAX)	31.02 (3.0 - 73.6)	50.88 (9.0 - 75.8)	17.99 (2.9 - 40.9)	29.68 (2.9 - 75.8)
RELATIVE DOSE INTENSITY				
>= 110%	1 (1.6)	0	0	1 (0.4)
90% TO < 110%	54 (85.7)	61 (76.3)	83 (85.6)	198 (82.5)
70% TO < 90%	6 (9.5)	16 (20.0)	12 (12.4)	34 (14.2)
50% TO < 70%	2 (3.2)	3 (3.8)	2 (2.1)	7 (2.9)
< 50%	0	0	0	0

Of the 97 patients treated in Cohort C, 51 were excluded due to not having a post-baseline serum nivolumab measurement. The remaining Cohort C patients represent a significant proportion of the patients included in the safety analysis (46/193, 24%), despite having the lowest exposure and shortest duration of treatment. Assuming that Grade 3+ events are more likely to occur with longer treatment, inclusion of patients from Cohort C in the analysis may cause 'dilution' of the results.

The distribution of $C_{avg,ss}$ for the analysis was not provided, except for the following summary.

Table 15. Distribution of $C_{avg,ss}$, as shown by the summary statistics

Subject Characteristic		CA209039 (n = 23)	CA209205 (n = 170)	Overall (n = 193)
Cavgss [mcg/mL]	Mean (SD)	101.387 (29.452)	116.737 (29.296)	114.908 (29.660)
	Median	95.500	117.000	116.000
	Min, Max	42.80, 152.00	29.60, 206.00	29.60, 206.00

Subjects who did not experience a Grade 3+ DR-AE event within 100 days of receiving their last treatment were censored (at the last dose date + 100 days) for the analysis (considered not to have had a Grade 3+ DR-AE). A total of 5 patients in Study CA209039 (22%) and 29 patients in Study CA209205 (17%) had Grade 3+ AEs reported.

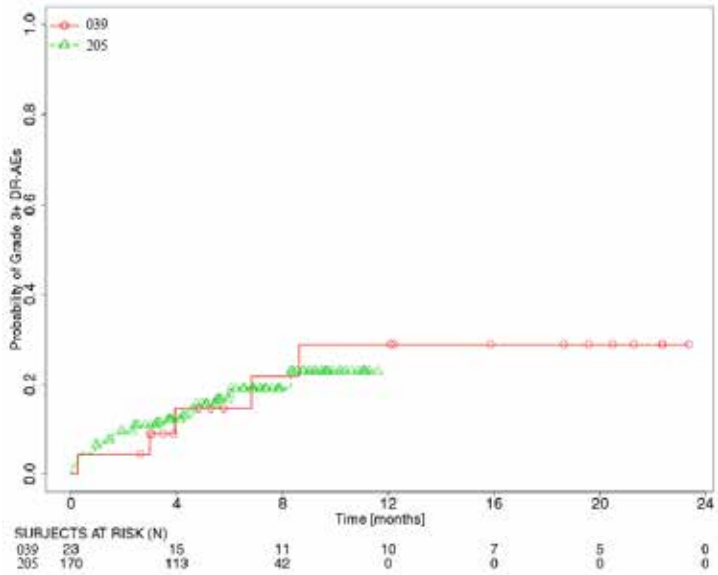
There were 5 subjects that had more than one Grade 3+ DR-AE reported on the same date

- One patient had Grade 3 elevation of liver enzymes ALP, γGT, ALT, AST
- One patient had elevated amylase and lipase
- One patient had elevated ALT and AST
- One patient had both pericardial effusion and pneumonia.

According to the report, for subjects with multiple events on the same date, only the first event included in the dataset was used for the analysis.

A Kaplan-Meier analysis of the probability of Grade 3+ DR-AEs versus time, by study, was provided.

Figure 12. K-M Plot of probability of Grade 3+ AE by duration of treatment

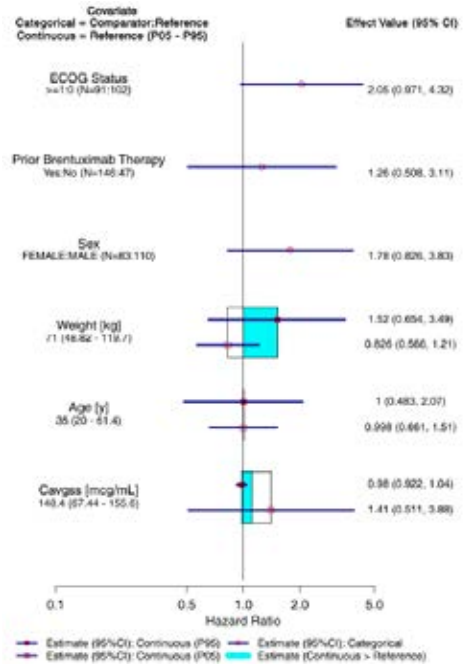


Comment: From the K-M analysis, the probability of Grade 3+ events appears to increase with duration of exposure, with this plateauing at 8 to 12 months. The plateau may be an effect of small patient numbers, as it is evident from this graphic that there were very few patients included in the analysis in whom treatment with nivolumab continued for longer than around 8 months. This is consistent with the timing of the analyses: with the interim analysis of Study CA209205 performed after a median duration of follow-up of 8.9 months for Cohort B and the interim analysis of Study CA209039 performed after median follow-up of 23 months.

The analysis reported that:

- Baseline weight, age, sex, and prior brentuximab therapy were not found to be significant predictors of the risk of Grade 3+ DR-AEs in patients with cHL.
- Exposure, as measured by $C_{avg,ss}$, was also not assessed as a significant predictor of Grade 3+ DR-AEs, as indicated by the hazard ratio coefficient of 0.7949 (95% CI 0.2219, 2.847).

Figure 13. Estimated covariate effects of E-R Grade 3+ DR-AEs (Full model)



According to the report, the covariate ECOG status was a significant predictor of experiencing a Grade 3+ DR-AE in the final model. A subject with ECOG score ≥ 1 was 2.142 times more likely to experience a Grade 3+ DR-AE compared to a subject with ECOG status of 0.

Comment: Patients with ECOG >1 were excluded from the studies. The conclusion should be that 'A subject with ECOG score of 1 was 2.142 times more likely to experience a Grade 3+ DR-AE compared to a subject with ECOG status of 0'. The possible effect of a worse ECOG score (> 1) is unknown.

Evaluator conclusions regarding the E-R safety analysis

The evaluator does not find the conclusions of this analysis convincing for the following reasons:

1. Inclusion of patients from Cohort C of Study CA209205. Due to staggered recruitment into the study, with later recruitment of Cohort C patients, the brief duration of treatment in Cohort C patients would result in reduced Grade 3+ AEs in this group (as shown by the K-M curve in Figure 12, above) and could dilute the results.
2. There were very few patients included in the analysis in whom treatment was continued for more than 8 months. The rate of Grade 3+ AEs in patients with cHL who receive treatment with nivolumab for longer than 8 months is unknown.
3. The E-R efficacy analysis report expressed concern that the relationship between efficacy and exposure may be unreliable '*due to the limited range of exposures in the analysis data, as all subjects were assigned the same nivolumab dosing regimen of 3 mg/kg Q2W'.* This same concern also applies to the E-R Safety analysis.

5.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

No investigations of genetic-, gender- and age-related differences in pharmacodynamics response were presented or described, apart from E-R analyses described above.

5.2.6. Immunogenicity

The assessment and reporting of clinical immunogenicity and therapeutic proteins has been recently reviewed by a group including representatives from industry, Health Canada and the FDA.[25] The following description of immunogenicity is based on this White paper.

Immunogenicity: Therapeutic proteins, including humanized or fully human mAb drugs, have the potential to induce immune responses ('immunogenicity'). The consequences of product immunogenicity vary from no evidence of clinical effect to severe, life-threatening responses. Because most of the adverse effects resulting from elicitation of an immune response to a therapeutic protein product appear to be mediated by humoral mechanisms, circulating antibody has been the chief criterion for defining an immune response to this class of products. By definition, these antibodies bind to the therapeutic product forming immune complexes. This may trigger immune-mediated reactions, anti-drug antibodies (ADA) have been implicated in infusion reactions and anaphylaxis, and may cause immune complex-mediated diseases. ADA have also caused secondary treatment failures (loss of efficacy). This may be due to inhibition of the pharmacological activity resulting from binding of the ADA to the product, 'neutralising ADA'. The binding of ADA may have no effect on efficacy but may alter the pharmacokinetics, for example by reducing clearance.

The incidence of ADA and their clinical sequelae can vary greatly between same-class products and between patient populations. These differences may be due to disparate bioanalytical methods and interpretation approaches as well as product-specific and patient-specific factors.

[25] Shankar G, et al. Assessment and Reporting of the Clinical Immunogenicity of the Therapeutic Proteins and Peptides - Harmonized Terminology and Tactical Recommendations. The AAPS Journal 2014.

ADA detection is complex as the analysis method used needs to be able to detect free ADA, ADA bound to the product in the patient's blood sample and ADA bound to other immunoglobulins in the patient's blood (for example: rheumatoid factor, soluble drug target). The biologic drug itself may also interfere with ADA detection, producing inaccurate results. The choice of control, the number of 'wash steps', the use of 'acid pre-treatment' of the sample to break apart ADA-drug immune complex, the process of serial dilution to determine changes in ADA titres over time can all affect the results obtained by the bioanalytic assay and, therefore, the interpretation of immunogenicity. As the white paper states: '*Due to such caveats, the US Food and Drug Administration (FDA) requires that biological product package inserts explicitly state that cross-product comparisons of immunogenicity can be misleading due to methodological differences and are therefore inappropriate.'* Determining if ADAs are neutralising or not can also be problematic. Neutralising antibody test methods, particularly cell-based bioassays, are often limited by sensitivity compared to ADA detection immunoassays; a lack of neutralising activity in these assays does not necessarily confirm that the ADA is non-neutralizing.

Immunogenicitiy and nivolumab: The sponsor's Integrated Pharmacometric Analysis Report provides information regarding the ADA detection methods used in the nivolumab clinical development programme. These have all been based on a qualitative, bridging ECL immunoassay, which is reported to be capable of detecting all antibody isotypes (IgG, IgM, IgE, IgA). Of note is that the assays used have evolved over time:

- The initial ECL assay (STM 4669) lacked a confirmatory testing step (Study MDX1106-01)
- The assay ECL (ICDIM 44 V3.00), a 3-tiered testing approach (screen, confirm, and titre) with an improved drug-tolerant method that included a sample pre-treatment step prior to analysis was used in Studies MDX1106-03 (CA209003) and CA209010.
- The most recent assay described (ICDIM 140), was further enhanced resulting in a drug tolerant assay exceeding the expected drug trough levels with the recommended nivolumab dosing regimen of 3 mg/kg IV Q2W. This assay was used in Studies CA209025, CA209063, CA209017, CA209057, CA209039, and CA209205.

Table 16. ADA assay methods

Validated Method	ECL (STM 4699) 1st Generation Assay	ECL-SPE/AD (ICDIM 44 V3.00) 2nd Generation Assay	ECL-BE/AD (ICDIM 140) 3rd Generation Assay
Species and Matrix	Human Sera	Human Sera	Human Sera
Analyte	Anti-nivolumab antibody	Anti-nivolumab antibody	Anti-nivolumab antibody
Testing	Screen	Screen, confirm, and titer	Screen, confirm, and titer
Positive Control	Anti-human IgG sera	Affinity purified anti-nivolumab	Affinity purified anti-nivolumab
Sensitivity	ND	50 to 100 ng/mL	6.25 to 12.5 ng/mL
Drug Tolerance (250 ng/mL Anti-Nivolumab Antibody)	ND[a]	Up to 12.5 µg/mL nivolumab	Up to 800 µg/mL nivolumab
Studies in Which Method Was Used	MDX1106-01 (CA209-001)	MDX1106-03 (CA209003) and CA209010	CA209025, CA209063, CA209017, CA209057, CA209039, and CA209205

Source: Study Validation Reports for STM 4699,[27] Validation Reports for ICDIM 44 V3.00,[28] Validation Reports for ICDIM 140[29]

[a] ≥ 1 µg/mL of drug suppressed the signal of the non-drug specific positive controls to below the cutpoint.

To classify the ADA status of a subject in a clinical study, each sample from the subject is categorised, using an in vitro test method, and then the subject's status is categorised. The definitions used in this categorisation are described in the sponsor's Core Immunogenicity Statistical Analysis Plan and common to studies in the clinical development programme, including Studies CA209039 and CA209205.

Definitions of sample ADA status categories:

- Baseline ADA-positive sample: ADA is detected in the last sample before initiation of treatment.
- Baseline ADA-negative sample: ADA is not detected in the last sample before initiation of treatment.
- ADA-positive sample: After initiation of treatment
  - an ADA detected (positive seroconversion) sample in a subject for whom ADA is not detected at Baseline; or
  - an ADA detected sample with ADA titre to be at least 4 fold or greater (>) than baseline positive titre.
- ADA-negative sample: After initiation of treatment, ADA not positive sample relative to Baseline.

Definitions of subject ADA status categories (Note: 16 weeks was chosen based on a long half-life of IgG4):

- Baseline ADA-positive subject: A subject with baseline ADA-positive sample
- ADA-positive subject: A subject with at least one ADA positive-sample relative to Baseline at any time after initiation of treatment:
  - Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart
  - Not PP-Last Sample Positive: Not persistent positive with ADA-positive sample at the last sampling timepoint
  - Other Positive: Not persistent positive but some ADA-positive samples with the last sample being negative
  - Neutralising Positive: At least one ADA-positive sample with neutralizing antibodies detected.
- ADA-negative subject: A subject with no ADA-positive sample after the initiation of treatment.

These definitions are in keeping with the White Paper on Immunogenicity referred to above.[25] This refers to 'treatment-boosted' titres in baseline ADA-positive subjects where the ADA titre is greater than the baseline titre by '*a scientifically reasonable margin, such as fourfold or ninefold*' with this representing twice the dilution level used in determining the titre. The following discussion is provided to support the choice of 16 weeks between positive samples for the definition of 'persistent positive': '*Because natural (endogenous) human IgG1, IgG2, and IgG4 have approximate half-lives in the range 21–25 days, five half-lives are approximately equal to 16 weeks. If an ADA were induced and never restimulated or boosted (a 'transient' antibody) so that it would be subject to its natural clearance mechanisms, then the ADA is expected to be eliminated at the end of five half-lives (actually, only a negligible 3% remains)*'

The Summary of Clinical Pharmacology provides a summary of ADA status as reported in different studies in the Clinical Trials program (see Table 17, below). This shows considerable variability in the incidence of subjects who are baseline positive and subjects who meet the definitions of ADA positive during treatment. The incidence of subjects who meet the definition of 'persistent positive' is uniformly low.

Table 17. Summary of nivolumab ADA using ICDIM 140 in nivolumab monotherapy

	Number of Subjects (%)									
Study Number (CA209)	063[a] (N=101)	037[a] (N=181)	066[a] (N=107)	017[a] (N=109)	057[a] (N=251)	067[a] (N=288)	025[b] (N=371)	039[c] (N=19)	205[d] (N=159)	Pooled Summary (N=1586)
Baseline ADA Positive	11 (10.9)	9 (5.0)	3 (2.8)	8 (7.3)	18 (7.2)	10 (3.5)	10 (2.7)	3 (15.8)	7 (4.4)	79 (4.98)
ADA Positive	12 (11.9)	13 (7.2)	6 (5.6)	21 (19.3)	43 (17.1)	33 (11.5)	27 (7.3)	1 (5.3)	1(0.6)	157 (9.9)
Persistent Positive	0	0	0	1 (0.9)	0	0	1 (0.3)	0	0	2 (0.1)
Only Last Sample Positive	8 (7.9)	9 (5.0)	2 (1.9)	4 (3.7)	12 (4.8)	10 (3.5)	7 (1.9)	1(5.3)	1(0.6)	54 (3.4)
Other Positive	4 (4.0)	4 (2.2)	4 (3.7)	16 (14.7)	31 (12.4%)	23 (8.0)	19 (5.1)	0	0	101 (6.4)
Neutralizing ADA Positive	0	2 (1.1)	0	3 (2.8)	3 (1.2%)	1 (0.3)	0	0	0	9 (0.6)
ADA Negative	89 (88.1)	168 (92.8)	101 (94.4)	88 (80.7)	208 (82.9)	255 (88.5)	344 (92.7)	18 (94.7)	158 (99.4)	1429 (90.1)

Note: Persistent positive subject defined as a subject with ADA-positive samples at 2 or more consecutive time points, where the first and last ADA positive samples were at least 16 weeks apart.

Additional information is available in the interim CSRs regarding the patients who were ADA positive in Studies CA209205 and CA209039.

There were 7/159 (4.4%) of patients in Study CA209205 and 3/19 (15.8%) of patients in CA209039 who tested positive for nivolumab ADA without prior exposure to nivolumab, with titres ranging from 1 to 4. Of these 10 patients:

- 8/10 patients were ADA negative on all subsequent testing, with this subsequent testing performed within 16 weeks of the baseline test
  - In Study CA209039, one of these patients had a baseline titre of 8 with 4 samples over the next 5 months all testing negative. The other patient had a baseline titre of 4 and 2 tests, 2 weeks and 8 weeks later, were both negative.
  - In Study CA209025, the baseline titres ranged from 1 to 4 and were negative at repeat testing approximately one month later in 6 patients.
- 1 patient in CA209039 was ADA positive at Baseline, with a titre of 4. The patient was subsequently tested on 5 occasions. On the first four occasions, ADAs were detected but not in a titre four-fold greater than baseline (titres 4, 2, 4 and 8). On the final occasion, the titre was 32, meeting the definition for 'ADA positive'. The patient was not 'persistent positive' as there were not 2 'ADA positive' samples 16 weeks apart.
- 1/10 had not had any subsequent testing.

In the two studies, there was only one patient who tested ADA positive on treatment. This patient from Study CA209205 had 3 samples were tested for ADA: the baseline was negative, the sample one month later had a titre of 4 and the third sample (approximately 8 weeks later) had a titre of 1. No specimens tested positive for neutralising antibodies. No subsequent testing was performed in this patient. The patient did not meet the definition of persistent positive as the two positive specimens were not 16 weeks apart. According to the brief narrative provided for this patient, he/she developed a Grade 1 rash at Day 169 (this was not considered to be a hypersensitivity reaction) and had the BOR of PR.

The Summary of Clinical Pharmacology provides a summary of select adverse events in the hypersensitivity/infusion reaction category by ADA Status (positive or negative) for those subjects who were treated with nivolumab monotherapy and in whom the ICDIM 140 ADA assay was used. Data was available from Studies CA209063, CA209037, CA209066, CA209017, CA209057, CA209067, CA209025, CA209039 (cHL all), and CA209205 (Cohorts A + B + C).

Table 18. Summary of hypersensitivity/infusion reactions by nivolumab ADA status

Select AE Category: Hypersensitivity/Infusion Reaction	Number of Subjects (%)	
	Nivolumab ADA Positive (N = 167)	Nivolumab ADA Negative (N = 1468)
Total Subjects with an Event	4 (2.4)	105 (7.2)
Anaphylactic Shock	0	1 (0.07)
Bronchospasm	1 (0.6)	10 (0.68)
Hypersensitivity	1 (0.6)	42 (2.9)
Infusion Related Reaction	2 (1.2)	58 (4.0)

Note: Integrated data from studies CA209063, CA209037, CA209066, CA209017, CA209057, CA209067 (monotherapy arm), CA209025, CA209039 (all cHL), and CA209205 (Cohort A+B+C)

This data was interpreted by the sponsor as: '*Overall, an association was not established between the presence of ADA and hypersensitivity or infusion reactions, suggesting that ADA does not alter the safety profile of nivolumab.*'

Of note, however, is that a total of 9.4% of patients had hypersensitivity/infusion reactions reported with these ranging from anaphylactic shock to minor infusion related reactions. Apart from noting that these reactions were not related to ADA status, there was no discussion regarding aetiology of these reactions.

Comment: It is not clear to the evaluator that the immunogenicity of nivolumab has been fully characterised. This may reflect a broader lack of knowledge regarding the immunogenicity of therapeutic proteins as the sponsor's summaries of immunogenicity appear to be in keeping with the recommendations of the White Paper.[25] However, it may also in part be due to assay used for nivolumab ADA being unreliable. Of concern to the evaluator are:

1. The highly variable incidence of patients who have antibodies to nivolumab present prior to exposure to nivolumab across different studies (reported range of incidence rates 2.8% to 15.8%). This does not appear to be related to cancer type as the two studies of patients with cHL, Studies CA209205 and CA209039, had baseline rates of 4.4% and 15.8% respectively. These reported rates of ADA prior to exposure may indicate an overly sensitive and unreliable assay. No discussion of the presence of ADA prior to exposure is provided by the sponsor.
2. The highly variable incidence of patients who test ADA positive on treatment across different studies, with this ranging from 0.6% to 19.3%. This does not appear to be related to cancer type as the two studies of patients with cHL, Studies CA209205 and CA209039, had ADA positive results of 0.6% and 5.3% respectively. No discussion of this variability across studies is provided by the sponsor.
3. The inconsistent appearance and disappearance of ADA, for example of the 10 patients in Studies CA209205 and CA 209039 who were baseline ADA positive, 8 were subsequently negative at repeat testing less than 16 weeks later.
4. According to the sponsor's table above, total of 109/1468 (9.6%) of patients receiving nivolumab monotherapy experienced a hypersensitivity/infusion reaction. No discussion of the cause of these reactions is provided by the sponsor, other than stating that they are not due to ADA. The evaluator is of the opinion that this capacity for nivolumab to trigger an immediate immune-mediated reaction needs further exploration. It may be that the ADA assay used is unreliable or that there is another element in the administered medication that is causing the reactions.

Of note is that there was a higher incidence of hypersensitivity/infusion reactions reported in the two studies in patients with cHL compared to the studies in patients with solid tumours: 26/158 (16.5%) of patients from all cohorts in Study CA209205 and 4/23 (17.4%) of patients in Study CA209039. None of these patients were ADA positive (see also 'Hypersensitivity events/infusion related reactions in Section 8.7 below).

5.2.7. Pharmacodynamic interactions

No investigations of pharmacodynamics interactions were presented or described. Patients receiving immunosuppressive therapy/therapies or with active auto-immune diseases were excluded from the studies. Patients who developed irARs during or following treatment could be treated with immune-suppressive therapy/therapies. A separate efficacy analysis has not been provided for these patients (see Question 15: Pharmacodynamic interactions in Section 11, below).

5.3. Evaluator's overall conclusions on pharmacodynamics

The sponsor has provided limited new pharmacodynamics information in this submission, with this including:

- efficacy analyses of variables related to baseline biomarker status (PD-L1 expression on R-S cells, 9p24.1 status) in patients with cHL
- some information regarding the time course of tumour response
- some information regarding the relationship between drug exposure and effect, with this based on two pharmacometric analyses
- an analysis of immunogenicity in patients with cHL.

5.3.1. Efficacy according to PD-L1 status and the presence of 9p24.1 chromosomal abnormalities

Study CA209205 reported the results of efficacy analyses according PD-L1 expression on R-S cells and 9p24.1 chromosomal abnormalities. Study CA209039 reported the results of efficacy analyses according PD-L1 expression on R-S cells and 9p24.1 chromosomal abnormalities (polysomy, gain, or amplification); PD-L1 and PD-L2 status by 'DFCI assay', pSTAT3 status by 'DFCI assay' and EBV status.

Both Study CA209039 and Study CA209205 used a different definition of PD-L1 expression compared to that used in solid tumours. In the cHL studies, PD-L1 expression was estimated according to the expression on R-S cells, but with no lower limit on the number of R-S cells per field. In solid tumours, PD-L1 expression was estimated according to the expression on tumour cells, with a minimum of 100 assessable tumour cells per slide.

Both studies found high PD-L1 expression in those patients for whom there were PD-L1 quantifiable specimens. Both studies also found that all patients for whom there were 9p24.1 quantifiable specimens, had at least one 9p24.1 chromosomal abnormality (polysomy and/or copy number gain and/or amplification). These findings suggest that R-S cells commonly express P-L1 and that 9p24.1 chromosomal abnormalities are common in cHL but firm conclusions cannot be drawn due to the high proportion of missing results.

Table 19. Summary of biomarker measurements in Studies CA209205 and CA209039

	Study CA209205 n = 80	Study CA209039 n = 23
Patients with PD-L1 quantifiable specimens, n (% of total patients)	63 (78.8%)	10 (43.5%)

	Study CA209205 n = 80	Study CA209039 n = 23
Patients with PD-L1 expression ≥ 1%, n (% of quantifiable patients)	57 (90.5%)	9 (90%)
Patients with 9p24.1 evaluable specimens, n (% of total patients)	45 (56.3%)	10 (43.5%)
Patients with at least one 9p24.1 chromosomal abnormality, n (% of evaluable patients)	45 (100%)	10 (100%)

Study CA209205 found no significant difference in outcome (ORR by IRRC) between PD-L1 positive and PD-L1 negative patients, using the cut-off of 1%: the ORR in PD-L1 positive patients was 66.7% (95% CI: 52.9, 78.6) compared to 83.3% (95% CI: 32.9, 81.6) in PD-L1 negative patients. However, this result should be interpreted with care due to missing results (PD-L1 quantifiable specimens were not available for 17/80 patients and to the small numbers of PD-L1 negative patients (6/63) to act as comparators. The analysis of efficacy according to 9p24.1 chromosomal abnormalities found that 45 patients had quantifiable specimens available; all 45 had at least one abnormality of 9p24.1. Analysis of efficacy according to this chromosomal abnormality was, therefore, not possible.

For Study CA209039, no conclusions can be drawn from the reported results due to the high proportion of missing results: only 10/23 patients had evaluable or quantifiable specimens for PD-L1 expression and 9p24.1 chromosomal abnormalities.

5.3.2. Time course of tumour response

In both studies of patients with cHL, all patients who responded to nivolumab showed this response (using the IWG criteria and IRRC assessment) within 6 months of commencing treatment. Over half of the patients who responded (55%, 58%) showed this response at the first scheduled tumour response assessment at 9 weeks. The time to response ranged from 9 weeks to 6 months.

Both Study CA209205 and Study CA209039 allowed patients with progression according to the IWG criteria to be continued on treatment at the discretion of the investigator, due to concerns regarding 'pseudoprogression'. It is thought that an initial increase in tumour size (or failure to decrease in size by the required amount) may occur with immune checkpoint inhibitors due to infiltration of the tumour by immune system cells and the associated inflammatory effect, rather than being due to tumour progression.

During Study CA 290205, there were 23 patients who had progressed, according to the 2007 IWG criteria as assessed by the investigators. Of these patients, 9 patients were continued on nivolumab treatment with the duration of treatment beyond progression ranging from 0.5 to 6.4+ months. Of these 9 subjects, 6 maintained tumour reduction in the target lesion although all developed new lesions. In Study CA209039, there were 4 patients were treated beyond disease progression. According to the definition of BOR per investigator, 3 of these subjects were subsequently classified as responders (PR). In 2 of the 3 responders, disease progression subsequently occurred and nivolumab treatment was ceased. In the other patient, treatment was discontinued and an allo-SCT performed. It is not clear from these findings that 'pseudoprogression' can be said to occur in patients receiving nivolumab for relapsed/refractory cHL.

5.3.3. Relationship between drug exposure and effect

The submission included two Exposure-Response analyses of nivolumab: an Exposure-Response Efficacy Analysis and an Exposure-Response Safety Analysis. In both analyses, the

exposure was determined by the Cavgss, with this calculated from the PK simulation. Of note is that the analyses include different populations of subjects: the PPK study and the E-R Safety analysis both include all 23 subjects from Study CA209039 and 170 subjects from Study CA209205 (from Cohorts A, B and C); the E-R Efficacy analysis includes 15 subjects from Study Ca209039 and 77 patients from Cohort B in Study CA209205 (only those patients with cHL who had failed both ASCT and brentuximab vedotin). In Study CA209205, recruitment was staggered, with recruitment to Cohort C occurring after recruitment to Cohort B was complete. The duration of treatment for each cohort at the time of the interim analysis could be considerably different with many patients in Cohort C having only received 1 to 2 doses.

The Exposure-Response Efficacy Analysis found that the variables of sex, age, BW, ECOG status, and number of prior therapies did not appear to affect the Pr(OR). The exposure to nivolumab did appear to affect Pr(OR) according to IRRC assessed OR: the Pr(OR) was predicted to be approximately 36% lower for a subject with $C_{avg,ss}$ at the 5th percentile (67.03 µg/mL) compared to a subject with the median $C_{avg,ss}$ (148.4 µg/mL). However, there was minimal difference for a subject with $C_{avg,ss}$ at the 95th percentile (161.9 µg/mL) compared to a subject at the median $C_{avg,ss}$, suggesting a flat range in the exposure-response curve at higher concentrations.

The report also noted that, due to the decreased CL, the average nivolumab exposure in cHL subjects was increased by approximately 43% relative to solid tumour subjects. This increased exposure was not considered clinically relevant with regard to efficacy as, at higher exposures, the Pr(OR) was in the '*flat range of the E-R curve*' regardless of the assessment modalities.

The report expressed concern that the relationship between efficacy and exposure may be unreliable '*due to the limited range of exposures in the analysis data, as all subjects were assigned the same nivolumab dosing regimen of 3 mg/kg Q2W and the sensitivity analysis indicated that only a few subjects were influential in explaining the discrepancy between the E-R results with IRRC- and investigator-assessed OR'.*

The Exposure-Response Safety Analysis reported that:

- Baseline weight, age, sex, and prior brentuximab therapy were not found to be significant predictors of the risk of Grade 3+ DR-AEs in patients with cHL
- The covariate ECOG status was found to be a significant predictor of experiencing a Grade 3+ DR-AE as a subject with ECOG score of 1 was twice as likely to experience a Grade 3+ DR-AE compared to a subject with ECOG status of 0. Patients with ECOG > 1 were excluded from all of the clinical studies.
- Exposure, as measured by $C_{avg,ss}$, was not assessed as a significant predictor of Grade 3+ DR-AEs, as indicated by the hazard ratio coefficient of 0.7949 (95% CI 0.2219, 2.847)

A K-M analysis (see Figure 12. K-M Plot of probability of Grade 3+ AE by duration of treatment, above) shows that the probability of Grade 3+ events appears to increase with duration of treatment, with this plateauing at 8-12 months. The plateau may be an effect of small patient numbers, as there were very few patients included in the analysis in who treatment with nivolumab continued for longer than around 8 months.

As with the Exposure-Response Efficacy analysis, the conclusions from this analysis should be interpreted with care due to '*the limited range of exposures in the analysis data, as all subjects were assigned the same nivolumab dosing regimen of 3 mg/kg Q2W',* the small number of patients who received nivolumab treatment for longer than 8 months and the inclusion of patients from Cohort C who had minimal exposure to nivolumab.

5.3.4. Analysis of immunogenicity

Only one patient in each of Studies CA209205 and CA209039 tested ADA positive state during treatment with nivolumab. However, there were 7/159 (4.4%) of patients in CA209205 and 3/19 (15.8%) of patients in CA209039 who tested positive for nivolumab ADA without prior

exposure to nivolumab. Of these 10 patients, 8 had no ADA detected on all subsequent testing, with this subsequent testing performed within 16 weeks of the baseline test; one patient had ADA detected on subsequent occasions but did not meet the criteria for 'persistent ADA positive'; one patient had no subsequent testing performed.

A substantial number of patients were reported to have hypersensitivity/infusion reactions in the two studies in patients with cHL: 26/158 (16.5%) of patients from all cohorts in Study CA209205 and 4/23 (17.4%) of patients in Study CA209039. None of these patients were ADA positive. This rate is higher than that reported in patients with solid tumours although it is not clear as to whether this is a real difference or an anomalous result due to the small number of enrolled patients

The Summary of Clinical Pharmacology provides a summary of select adverse events in the hypersensitivity/infusion reaction category by ADA Status (positive or negative) for those subjects who were treated with nivolumab monotherapy in the clinical development programme and in whom the same ADA assay was used (see Table 18, above).

This data was interpreted by the sponsor as: '*Overall, an association was not established between the presence of ADA and hypersensitivity or infusion reactions, suggesting that ADA does not alter the safety profile of nivolumab.*' Of note, however, is that a total of 9.4% of patients had hypersensitivity/infusion reactions reported with these ranging from anaphylactic shock to minor infusion related reactions. Apart from noting that these reactions were not related to ADA status, there was no discussion regarding aetiology of these reactions.

It is not clear to the evaluator that the immunogenicity of nivolumab has been fully characterised. This may reflect a broader lack of knowledge regarding the immunogenicity of therapeutic proteins as the sponsor's summaries of immunogenicity appear to be in keeping with White Paper recommendations.[25] Of concern to the evaluator are:

1. The highly variable incidence of patients who have antibodies to nivolumab present prior to exposure to nivolumab across different studies (reported range of incidence rates 2.8% to 15.8%). This does not appear to be related to cancer type as the two studies of patients with cHL, Studies CA209205 and CA209039, had baseline rates of 4.4% and 15.8% respectively.
2. The highly variable incidence of patients who test ADA positive on treatment across different studies, with this ranging from 0.6% to 19.3%. This does not appear to be related to cancer type as the two studies of patients with cHL, Studies CA209205 and CA209039, had baseline rates of 0.6% and 5.3% respectively.
3. The inconsistent appearance and disappearance of ADA, for example, of the 10 patients in Studies CA209205 and CA 209039 who were baseline ADA positive, 8 were subsequently negative at repeat testing less than 16 weeks later (within several half-lives of endogenous immunoglobulin).
4. According to the sponsor's table above, total of 109/1468 (9.6%) of patients receiving nivolumab monotherapy experienced and hypersensitivity/infusion reaction. No discussion of the cause of these reactions is provided by the sponsor, other than stating that they are not due to ADA. The evaluator is of the opinion that this capacity for nivolumab to trigger an immediate immune-mediated reaction needs further exploration and discussion.

5.3.5. Pharmacodynamic interactions

No investigations of pharmacodynamics interactions were presented or described. Theoretically, co-administration of immunosuppressive agents could reduce the efficacy of nivolumab. Patients receiving immunosuppressive therapy/therapies or with active auto-immune diseases were excluded from the studies. Patients who developed irARs during or following treatment could be treated with immune-suppressive therapy/therapies. A separate efficacy analysis for these patients has been requested. See Question 15: Pharmacodynamic interactions in Section 11, below.

Comment: The sponsor performed additional efficacy analyses on the patients who developed irARs during or following treatments and were being treated with immune-suppressive therapies for the SCE population from Studies CA209205 and CA209039 (Cohort B and ASCT-BREN failed group). This found a numerically lower ORR per IRRC in the 26 patients who received immunosuppressive therapy compared to the 69 who did not but substantial overlap of the 95% CI (57.7% (95% CI 36.9, 76.6) compared to 69.6% (95% CI 57.3, 80.1)). Median PFS was also lower in the sub-group treated with immunosuppression (11.33 months compared to 14.95 months. This is a post-hoc analysis of a small number of patients but does create uncertainty regarding a potential reduction in the efficacy of nivolumab when co-administration of immunosuppressive therapy is required.

6. Dosage selection for the pivotal studies

6.1. Study Design

Neither study presented in the submission is a Phase III study. Both were exploratory studies using open label, single arm parallel cohort designs. In both studies, interim analyses have provided the results reported in this submission.

6.1.1. Study CA209205

Study CA209205 is a Phase II single arm open label study that included patients with cHL who have failed with ASCT, divided into cohorts according to whether the patients had also received brentuximab vedotin, and the timing of this treatment. The primary outcome measure was objective response rate (ORR) according to IRRC using 2007 IWG criteria (see Table 1, at the start of this document). Cohort B in this study included the target population for the main part of the proposed indication - patients who have received brentuximab vedotin treatment as salvage following failure of ASCT.

According to the Study CA209205 protocol:

- *'A single-arm (i.e. non-comparative) study design was chosen because there is no appropriate, fully-approved active comparator for relapsed third-line or later cHL subjects failing ASCT'*
- *'A parallel cohort approach was selected because the target population of cHL failing ASCT requires clear distinction based upon prior brentuximab vedotin treatment" and "This study design will test nivolumab in parallel treatment groups; brentuximab vedotin-naïve patients (Cohort A) who have failed ASCT, or those who received brentuximab vedotin treatment as salvage following failure of ASCT (Cohort B). Cohort A or Cohort B represents the patients who require the third or fourth line of therapy.'*

Two additional cohorts have since been added to the original study design: Cohort C (prior ASCT and prior treatment with brentuximab vedotin at any time) and Cohort D (newly diagnosed cHL with these patients receiving combination therapy with nivolumab 240 mg every 2 weeks + doxorubicin/vinblastine/dacarbazine).

Analysis for all cohorts was originally planned to be after 12 months of follow-up. A late protocol amendment resulted in the analysis of the primary endpoint in Cohort B being performed after 6 months of follow-up from 'last patient first treatment' (LPFT). This protocol amendment occurred in June 2015 with database lock for the interim report in October 2015. The rationale provided for the change in duration of follow-up for cohort B was: *'In discussion with Food and Drug Agency (FDA) an analysis of these patients with minimum follow-up of 6 months after the last enrolled subject's first dose of study therapy will now be included. This analysis may be included in a future regulatory submission(s) if supportive of accelerated registration.'*

The interim report included efficacy results from Cohort B but safety, PK and some PD results from all Cohorts A, B and C. At the time of the interim analysis, the median duration of treatment had not been reached for any cohort. Due to staggered recruitment to the cohorts, the duration of follow-up varied for each cohort: median duration of follow-up was 5.1 months for Cohort A, 8.9 months for Cohort B; 2.8 months for Cohort C.

6.1.2. Study CA209039

This was a Phase I single arm dose escalation study of nivolumab 1 mg/kg or 3 mg/kg as monotherapy, or in combination with ipilimumab or lirilumab, with the intention of assessing the safety, tolerability, preliminary efficacy, and PK of nivolumab in subjects with a variety of relapsed or refractory haematologic malignancies (multiple myeloma, Hodgkin Lymphoma, primary mediastinal B cell lymphoma, B cell lymphoma, T cell lymphoma). The dose escalation phase was followed by an expansion phase, with patients divided into cohorts according to the underlying malignancy and the treatment regimen. The dose expansion phase included a subgroup of 23 patients with Hodgkin lymphoma in whom the dose of 3 mg/kg was used. By chance, all 23 patients had cHL.

Efficacy end-points were exploratory and included ORR, duration of response (DOR), CR and PR rates, time to CR and PR, and duration of CR and PR. Initially all tumour response end-points were investigator-assessed using criteria based on the protocol defined response criteria that included components of both the 1999 IWG criteria and the 2007 revised criteria (see Table 1, at the start of this document). A late protocol amendment that allowed retrospective collection of radiologic images for blinded independent central review resulted in the analysis of tumour response- dependent efficacy endpoints being performed retrospectively by an IRRC using 2007 IWG criteria. This protocol amendment occurred in April 2015, with database lock for the interim report in August 2015. The interim results, after a minimum follow-up of 18 months, of a 23 patient cohort were provided.

According to the SAP, this interim analysis was performed '*to support a regulatory filing for the treatment with nivolumab monotherapy of patients with relapsed or refractory cHL after failure of ASCT and subsequent brentuximab vedotin*'.

Comment: Neither of the studies presented are a 'pivotal' study: both of the studies are single arm and open label; both use a surrogate efficacy end-point; both provide 'early' data with relatively brief follow-up. In both studies, an unplanned interim analysis was performed after a late major protocol amendment. It would appear that these unplanned interim analyses were performed with the intention of supporting an early filing for regulatory approval. It is important to note that no confirmatory studies for the proposed indication are planned.

The following rationale for the submission was provided in the sponsor's cover letter:

> *'Justification for not providing Phase III randomised controlled clinical data:*
>
> *The evidence submitted with this application supports a very narrow indication for which it was not possible to recruit a sufficiently large number of patients to conduct a reasonably powered, randomised Phase III study. As a consequence [the sponsor] has not conducted nor is planning a confirmatory Phase III study in this precise patient population due to the small number of subjects available, the late stage of disease and the absence of registered comparator arm.*
>
> *[The sponsor] is however planning a Phase III trial in an earlier treatment line in subjects with cHL. Study design options are still being investigated.'*

6.2. Dose selection

The Summary of Clinical Pharmacology notes that: '*The recommended dose and schedule of nivolumab monotherapy for cHL is the same as that approved for melanoma, SQ NSCLC, and RCC monotherapy: 3 mg/kg IV infusion over 60minutes Q2W.'*

The rationale provided for this dosing schedule in the study protocol for Study CA209205 was that: '*The monotherapy dose and schedule of nivolumab 3 mg/kg Q2W was selected for Phase II/III studies across tumour types based upon an interim analysis on 24 February 2012 of safety, efficacy, and exposure-response data from approximately 300 subjects treated in the Phase I Study CA209003 (also known as MDX1106-03).'*

The rationale for the dosing schedules of 1 mg/kg and 3 mg/kg in the study protocol for Study CA209039 is that these were the doses evaluated in Study CA209003. Early versions of the study protocol for Study CA209039 included the dose of 10 mg/kg that was also used in Study CA209003. The study protocol also notes with respect to Study CA209003 that no MTD was identified and that *'Limited evaluation of efficacy in subjects with melanoma across the dose levels suggested there was a similar level of efficacy although the highest response rate was observed at the 3 mg/kg dose level. Ongoing studies will help to clarify the optimal dose and schedule for evaluation.'*

Comment: No results from the dose escalation phase of Study CA209039 have been provided with this submission.

Study CA209003 CSR was provided to the TGA with the first nivolumab NBE submission. In this dose-ranging study, patients with solid organ tumours (melanoma, renal cell carcinoma, NSCLC, colorectal cancer, prostate cancer) were treated at one of five dose levels (0.1, 0.3, 1.0, 3.0 and 10.0 mg/kg) with treatment was administered every 2 weeks, for up to 48 doses. Efficacy was determined by investigator-assessed tumour measurements using RECIST v1.0 criteria, and consisted primarily of the objective response rate (ORR). There was no apparent dose-response relationship across the evaluated dose ranges in subjects in the rate of objective responses for patients with melanoma or RCC although the response rate was greater in NSCLC subjects treated with 3 or 10 mg/kg nivolumab. The conclusion of this study recommended the dose of 3 mg/kg given two weekly for all cancer types.

Nivolumab dose selection for cHL appears to be based on generalisation from dosing in solid tumours with the underlying assumption that all tumours will respond similarly to nivolumab and that nivolumab in patients with any tumour type will have similar pharmacokinetics. The evaluator notes that, according to the PPK analysis provided with this submission, the pharmacokinetics of nivolumab in patients with cHL appear to differ from the pharmacokinetics in patients with solid tumours: patients with cHL appear to have reduced clearance of nivolumab and a corresponding increase in exposure.

7. Clinical efficacy

7.1. Study CA209205

Comment: Only efficacy results for cohort B are provided in the interim study report. However, the safety data provided includes all cohorts to DBL. Some information regarding all cohorts is therefore provided in this description.

7.1.1. Study summary

A brief summary of Study CA209205 is given in Table 20, below.

Table 20. Study CA209205 Summary

Study CA209205 Summary	
Study identifier	Study CA209205; ClinicalTrials.gov number: NCT02181738
Study title	Non-comparative, multi cohort, single arm, open label, Phase II study of nivolumab (BMS-936558) in classical Hodgkin lymphoma (cHL) subjects after failure of autologous stem cell transplant (ASCT).
Related publication	Younes A et al. Checkmate 205: Nivolumab (nivo) in classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and brentuximab vedotin (BV); A Phase II study. J Clin Oncol 34, 2016 (suppl; abstr 7535).
Design	Phase II open label, non-comparative, three cohort, single arm study of nivolumab monotherapy (3 mg/kg Q2W) in patients with cHL who received prior high dose conditioning chemotherapy and failed ASCT: · Cohort A: brentuximab vedotin-naïve · Cohort B: received brentuximab vedotin treatment as salvage after failure of ASCT · Cohort C: prior ASCT and prior treatment with brentuximab vedotin at any time *Note: Only the efficacy results for Cohort B are included in this interim study analysis.*
Patient group	Patients with relapsed/refractory cHL who received prior high dose conditioning chemotherapy and failed ASCT
Dates	Study initiation date 12 August 2014. The study is ongoing. Database lock for primary analysis of Cohort B was 20 August 2015 with the interim CSR dated 5 February 2016.
Location(s)	34 sites in 10 countries (Austria, Belgium, Canada, Czech Republic, Germany, Italy, the Netherlands, Spain, the United Kingdom, the United States).
Main eligibility criteria	Male and female subjects aged ≥ 18 years, ECOG performance status of 0 or 1 and with relapsed/refractory cHL after failure of ASCT who were: · naïve to brentuximab vedotin: Cohort A · who had prior brentuximab vedotin treatment after failure of ASCT: Cohort B · who had prior brentuximab vedotin treatment before and/or after failure of ASCT: Cohort C Biopsy confirmation of cHL prior to initiation of study drug was required. Patients with prior allogeneic SCT or CNS lymphoma were excluded.
Randomisation and blinding	Not applicable.

Study CA209205 Summary	
Study treatments	Study treatment was the same in each cohort: nivolumab 3 mg/kg every 2 weeks by IV infusion. Treatment was continued until disease progression, or discontinuation of study therapy in subjects receiving nivolumab beyond progression, discontinuation due to toxicity, or other reasons for discontinuation. Cohort C subjects who have had persistent CR for 1 year were to discontinue study treatment with the possibility to reinitiate treatment following a relapse. After treatment discontinuation, patients had 2 follow-up visits for safety assessments and collection of PK and immunogenicity samples; patients were followed for survival every 3 months.
Duration of follow-up	Primary analysis was to be performed separately for each cohort (i.e., at separate time-points) upon completion of a pre-specified minimum follow-up after last patient first treatment (LPFT). This was 6 months for cohort B (changed from 12 months with a late protocol amendment) and 12 months for other cohorts.
Primary efficacy outcome measure	ORR per IRRC using 2007 IWG criteria.
Secondary outcome measures	DOR, CR rate and duration of CR, PR rate and duration of PR as assessed by IRRC; Investigator assessed ORR and DOR.
Other measures	PFS per IRRC, OS Safety and tolerability Exploratory measures related to QoL, biomarkers, pharmacokinetics and pharmacodynamics.
No of subjects	At data cut-off date for this interim report, 276 subjects were enrolled in the study. Of the 276 subjects enrolled, 240 were treated with nivolumab across the 3 cohorts (63 in Cohort A, *80 in Cohort B*, and 97 in Cohort C).
Results for Cohort B	
Participant flow	80 patients were treated. At DBL, 51/80 of Cohort B were continuing in treatment. Of the 29 not continuing in treatment, 13 stopped due to disease progression, 4 due to nivolumab toxicity, 2 at subject request, 8 for 'other reason', 1 was lost to follow-up and one was not reported. There were five patients not continuing in the study: 1 had died, 2 withdrew consent and 2 were lost to follow-up, and one patient whose status in the study was 'not reported'.
Study drug exposure	The median number of cycles was 17 (range 3-25); 76% received ≥ 90% of planned dose intensity. The KM estimate of median duration of treatment was not reached for any cohort.
Results, demographics	The median age was 37 years with 3 subjects aged 65 years or older. Most subjects were white (88.8%) and male (63.8%). All subjects had a baseline ECOG PS of 0 or 1, 52.5% with ECOG PS of 1. The majority of the subjects (67.5%) had Stage IV disease at study entry.

Study CA209205 Summary	
Primary efficacy outcome	At time of analysis median duration of follow-up for Cohort B was 8.9 months (range 1.9, 11.7). BOR could not be determined in 3 subjects. ORR per IRRC = 66.3% (95% CI 54.8, 76.4) No of responders = 53 No with CR = 7/80 (8.5%), No with PR = 46/80 (57.5%) Median duration of response 7.8 months (95% CI 6.64, NA). Note: 31/53 responders per IRRC were still on treatment and censored prior to the median.
Secondary outcomes	PFS: median PFS per IRRC 9.99 months (95% CI 8.41, NA) OS: 3/80 deaths; 6 month OS rate 98.7% ORR per investigator: 72.5% (95% CI 61.4, 81.9) No of responders = 58 No with CR = 22/80, No with PR = 36/80.
Subsequent anti-tumour therapy	13/80 patients received subsequent anti-tumour therapy. Of these, 6 had SCT, 5 allo-SCT and 1 ASCT.
Objective Response per IRRC and PD-L1 expression	Objective response per IRRC with nivolumab in Cohort B subjects was observed regardless of baseline PD-L1 expression status.
HRQoL	Interpretation of these results is difficult due to the small numbers after Week 33 and in follow-up. *Cancer-related Quality of Life - EORTC-QLQ-30* According to the Summary of Clinical Efficacy: *'improvements from baseline were observed for: role function at Week 9 (mean change=10.7, SD 9.0), social function at Week 33 (mean change=10.6, SD 23.5), and insomnia at Week 33 (mean change=-12.2, SD 25.6). No clinically meaningful deterioration was observed in any of the EORTC QLQ-C30'* *Generic Health Status - EQ-5D VAS* The baseline score for the EQ-5D VAS for the Cohort B subjects was 61.9 (SD 30.5). The average EQ-5D VAS score increased over time and exceeded the average baseline score by more than the 7-point MID from Week 9 through Week 33.
Abbreviations: BOR: best overall response; CR: Complete remission; cHL: classical Hodgkin Lymphoma; DOR: duration of response; IRRC: Independent radiologic review committee ; IWG: International Working Group; ORR: objective response rate = CR+PR/total; OS: overall survival;PD-L1: programmed death-ligand 1; PFS: progression-free survival; PR: Partial remission.	
Comment: According to the information at clinicaltrials.gov, enrolment in Cohorts A, B and C is complete and a fourth cohort has been added, newly diagnosed cHL. These patients receive combination therapy with nivolumab 240 mg every 2 weeks + doxorubicin: 25 mg/m^2 + vinblastine: 6 mg/m^2 + dacarbazine 375 mg/m^2.	

7.1.2. Good Clinical Practice

The interim CSR states: *'The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good*

Clinical Practice, as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).'

Comment: the evaluator assumes that in the Subject ID format of CA209205-xx-yyy, the 2-digit xx number identifies the study site. If this assumption is correct, then 27/65 significant protocol deviations and 1/14 relevant protocol deviations occurred at Site 33 and 6/14 relevant protocol deviations occurred at Site 35. Significant protocol deviations were defined as study conduct that differed significantly from the protocol, including GCP noncompliance. Relevant protocol deviations were defined as having the potential to affect the interpretability of study results. At the above sites, the 'relevant protocol deviations' involved enrolment of patients without measurable disease. The number and variety of protocol deviations at Site 33 raise concerns regarding study conduct at this site. The number of inappropriately enrolled patients at site 35 raises concerns regarding study conduct at this site.

The efficacy results of this interim analysis of Study CA209205 are based on the results of the 80 patients in Cohort B of the study. From the by-subject listings provided in the appendices, 16 of the patients in Cohort B were treated at Site 33 and 5 patients at site 35. The sponsor is asked to provide an efficacy analysis with the patients from site 33 and site 35 excluded, or a justification for not doing so (see also Major protocol violations/deviations for this study later in this section and Question 18: Study conduct in Study CA209205 in Section 11, below).

7.1.3. Study objectives

According to the Statistical Analysis Plan, the research hypothesis of this study was:

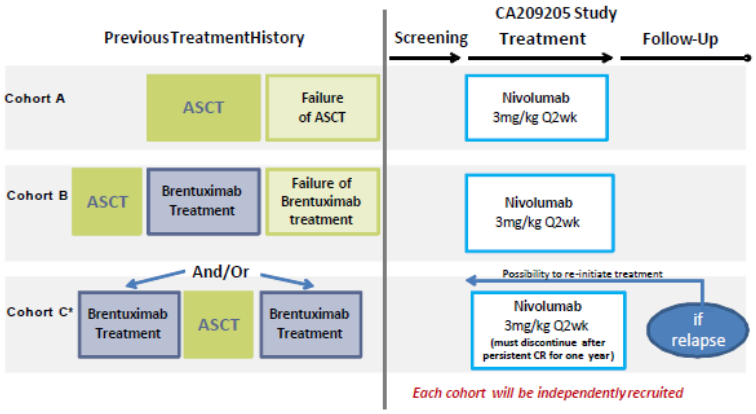
'Treatment with nivolumab will lead to clinical benefit, as demonstrated by a clinically meaningful objective response rate, including durable responses with substantial magnitude of tumor burden reduction in heavily treated cHL subjects.'

The primary objective of the study was to assess the clinical benefit of nivolumab, as measured by objective response rate (ORR) based on IRRC assessment, and defined as proportion of subjects achieving the Best Overall Response (BOR) of either a partial remission (PR) or complete remission (CR) according to the revised International Working Group criteria for Malignant Lymphoma (2007 IWG criteria).

7.1.4. Study design

Study design is shown in Figure 14, below.

Figure 14. Study design schematic for Study CA209205



*Cohort C: Subjects who failed ASCT and who have received prior treatment with brentuximab vedotin at any timepoint. Patients may have brentuximab treatment only before ASCT and failure of ASCT. Patients may have failure of ASCT, and failure of post-ASCT brentuximab treatment. Or, patients may have brentuximab treatment before and after ASCT, and failure of brentuximab at enrollment.

Primary analysis will be performed separately for each cohort (that is, at separate time points) upon completion of a pre-specified amount of follow-up after last patient first treatment (LPFT) as follows:

- Cohort A: Primary ORR analysis after 1 year minimum follow-up in all Cohort A subjects
- Cohort B: Primary ORR analysis after 6 months minimum follow-up in all Cohort B subjects
- Cohort C: Primary ORR analysis after 1 year minimum follow-up in all Cohort C subjects.

Analysis schedules were chosen *'based on a median duration of response (6.7 months) and a median duration of CR (20.5 months) observed from a pivotal Phase II study testing brentuximab vedotin in a similar patient population'*. Additional survival analysis will be conducted for up to 5 years beyond analysis of the primary endpoint.

The safety analyses will be performed on combined cohorts.

7.1.5. Protocol amendments

A number of protocol amendments occurred. Of these, the most significant were:

In June 2014:

- Change of the first time-point assessment to Week 9
- Allowance of study drug administration prior to the results of a bone marrow biopsy
- Allowance of continuation of study drug if 'non-conventional' response occurs and strict application of the 2007 IWG criteria would otherwise indicate 'disease progression'

In December 2014:

- Addition of Cohort C to allow for changing practices/regulatory approvals for the use of brentuximab vedotin in patients with cHL

In June 2015:

- Change in the duration of follow-up and timing of analysis for the primary end point. For Cohort B, the duration of follow-up was reduced from 12 months to 6 months with database lock for the primary end-point analysis then occurring in October 2015.

Comment: The rationale provided for the change in duration of follow-up for cohort B was 'In discussion with Food and Drug Agency (FDA) an analysis of these patients with minimum follow-up of 6 months after the last enrolled subject's first dose of study therapy will now be included. This analysis may be included in a future regulatory submission(s) if supportive of accelerated registration.' This early analysis will allow faster determination of favourable tumour response but will limit determination of how durable any responses may be and if tumour response translates into improved overall survival.

7.1.6. Inclusion and exclusion criteria

7.1.6.1. Main inclusion criteria

- Males and females aged ≥ 18 years who signed an informed consent form (ICF)
- Confirmed documentation of cHL after failure of ASCT or after failure of ASCT and brentuximab vedotin
- Cohort B: Subjects who failed treatment with brentuximab vedotin which was administered following failure of ASCT, and who met one of the following criteria according to the 2007 IWG criteria:
  - Documented failure to achieve at least PR after the most recent treatment; or
  - Documented relapse disease (after CR) or disease progression (after PR or SD)

- Measurable disease with at least 1 lesion that was > 15 mm (1.5 cm) in the longest diameter on cross-sectional imaging and measureable in 2 perpendicular dimensions on CT (or MRI) and FDG avid by positron emission tomography (PET)
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Prior high-dose conditioning chemotherapy followed by ASCT as a part of salvage therapy for cHL.

7.1.6.2. Main exclusion criteria

- Known central nervous system lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma (HL)
- Prior allo-SCT
- Active interstitial pneumonitis; active, known or suspected autoimmune disease
- Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration.
- Recent anti-tumour therapies, including radiation therapy
- Recent major surgery.

Comment: patients with interstitial pneumonitis were excluded for the study. First line treatment regimens for cHL include bleomycin. Interstitial lung disease is reported in up to 10% of patients treated with bleomycin. The sponsor is asked to provide an estimate of the proportion of cHL patients who would be excluded from the study due to interstitial pneumonitis and if this may affect the generalisability of the results of this study to the post-approval population.

7.1.7. Study treatments

Subjects underwent screening evaluations to determine eligibility within 28 days prior to first dose. A bone marrow biopsy/aspirate was performed at screening. Subjects received nivolumab 3 mg/kg IV on the first day of each 2 week cycle, with this treatment continued until unacceptable toxicity or disease progression, which was defined by relapsed disease (after CR achieved during the study) or progressive disease (after PR, stable disease (SD) attained during the study) according to the 2007 IWG criteria. Treatment beyond investigator-assessed progression was permitted.

The follow-up/observational period began when the decision was made to discontinue a subject from nivolumab treatment. After completion of the 2 scheduled initial follow-up visits, subjects were to be followed every 3 months (by clinic visit or telephone contact) for survival and report of any subsequent anti-cancer treatments until death, loss to follow-up, withdrawal of consent, or conclusion of study.

Radiographic tumour assessments were performed by computed tomography (preferred) or magnetic resonance imaging (MRI) at screening and on-treatment according to a pre-specified schedule. Assessments were continued until disease progression was documented, or until the subject initiated a preparative regimen for allogeneic stem cell transplant (allo-SCT) or ASCT, whichever occurred earlier.

Fluorodeoxyglucose (^{18}F) positron emission tomography (FDG-PET) scan was required in all subjects at screening and at Weeks 17 and 25. A FDG-PET scan at Week 49 was required for subjects who did not have two consecutive negative FDG-PET scans. After Week 1 and prior to Week 49, FDG-PET scan was also required for confirmation of a radiographic CR at other timepoints.

Subjects who discontinued study therapy for reasons other than disease progression or allo-SCT or ASCT were to continue to have radiographic assessments at the intervals described above

until disease progression, loss to follow-up, or withdrawal of study consent. For subjects who discontinued study therapy by proceeding to SCT, tumour assessments by the investigator were required after SCT; and acute and chronic graft-versus-host disease (GVHD) documentation was also simultaneously collected for the subjects who underwent allo-SCT.

The determination of tumour response to study treatment was made by the IRRC and investigators using 2007 IWG criteria. Tumour assessments for ongoing study treatment decisions were completed by the investigator using 2007 IWG criteria.

Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents were permitted in the absence of active autoimmune disease.

7.1.8. Efficacy variables and outcomes

7.1.8.1. Efficacy endpoints

Primary efficacy endpoint

The primary endpoint was ORR as determined by an IRRC according to the 2007 IWG criteria. This was to be assessed after 6 months minimum follow-up for Cohort B and 12 months for Cohorts A and C.

From the Statistical Analysis Plan:

'The ORR was defined as the number of subjects with a best overall response (BOR) of CR or PR based on IRRC assessment according to the 2007 IWG criteria divided by the number of treated subjects. The BOR was defined as the best response designation recorded between the date of first dose and the date of initial objectively documented progression per the 2007 IWG criteria or the date of subsequent anti-cancer therapy, whichever occurred first. Allogeneic SCT and ASCT will be considered as subsequent anti-cancer therapy. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial 2007 IWG defined progression. The objective response will be further characterised by the time to response (TTR), with this defined as the time from first dosing date to the date of the first response, based on IRRC assessment, and the duration of response (DOR).'

Secondary efficacy endpoints

These included: investigator-assessed ORR (according to 2007 IWG criteria and as defined for IIRC assessment); IRRC- and investigator-assessed durations of response (DORs) with DOR defined as the time from first response (CR or PR) to the date of initial objectively documented progression or death from any cause, whichever occurred first. Subjects who started any subsequent anti-cancer therapy without a prior reported progression were censored at the last tumour assessment prior to initiation of the subsequent anti-cancer therapy.

Additional secondary endpoints were CR rate, duration of CR, PR rate, and duration of PR based on IRRC assessments.

Exploratory efficacy endpoints

These included PFS per IRRC and OS.

7.1.8.2. Tumour response assessment

Each patient had regularly scheduled scans (CT/MRI and PET) performed for tumour response assessment (see Figure 15 and Table 21, below). At each timepoint the response was determined using the categories of CR, PR, SD and PD, as defined by the 2007 IWG criteria. The 'best overall response' (BOR) was ordered as CR, PR, SD then PD with allocation of BOR to the highest category observed for any time-point response for each patient.

Figure 15. Imaging (CT or MRI and FDG-PET scan) schedule for tumour response assessments

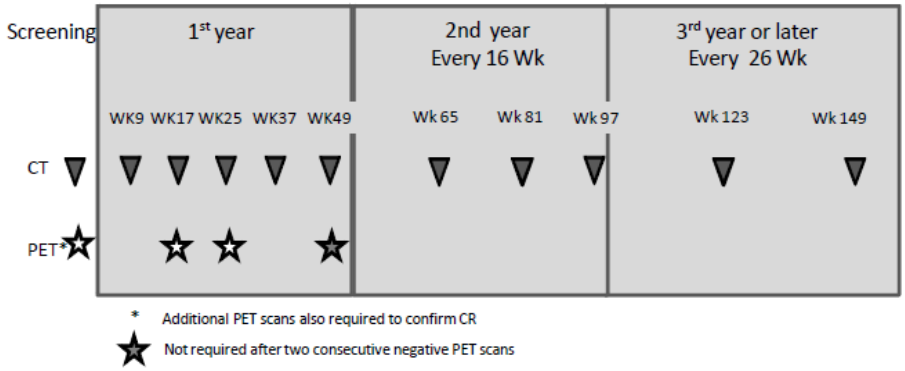


Table 21. Imaging schedule

Timepoint	Schedule	Imaging Data
Screening	Within 28 days prior to first dose	• CT (with contrast) or MRI (with contrast) of the chest, abdomen, pelvis and any other known sites of disease (e.g. neck) • FDG-PET
Treatment Phase	At Week 9 (± 7 days) after the start of therapy and then at Weeks 17, 25, 37 and 49 during the first year, then every 16 weeks (± 14 days) up to Week 97, then every 26 weeks (± 21 days) beyond Week 97, until disease progression is documented or until subject initiates a preparative regimen for allogeneic SCT or ASCT, whichever occurs earlier	• CT (with contrast) or MRI (with contrast) of the chest, abdomen, pelvis and any other known sites of disease (e.g. neck)† • FDG-PET*

* On-treatment FDG-PET scan will be required for all subjects at Weeks 17 and 25 (±7 days). Additionally, a FDG-PET scan at Week 49 (± 7 days) is required for subjects who do not have two consecutive negative FDG-PET scans after Week 1 and prior to Week 49. FDG-PET scan will also be required for confirmation of radiographic CR after initiation of the study drug at other timepoints where FDG-PET is not otherwise scheduled; this FDG-PET scan should be performed within 4 weeks of a CT scan.

† For Cohort C subjects: When Cohort C subjects discontinue study therapy due to persistent one year CR, CT (preferred) or MRI will be required for CR confirmation. These patients will then require CT (preferred) or MRI at the time of the first FU/Observational visit: 6 months (± 14 days) from last dose of study drug, or if clinically indicated (ie clinical evidence of relapse).

Tumour response assessment by IRRC

The company providing IRRC services was responsible for investigation site qualification and independent determination of time-point responses. Site qualification involved review of a completed site survey to ensure that the site had appropriate imaging capabilities. The quality of images and completeness of data as received by the IRRC were audited during the study. Independent determination of time-point responses was by radiological and then oncological review. CT/MRI and PET scans were independently reported by two radiologists using the 2007 IWG criteria. If these reports were discordant, the scans were reviewed by a third radiologist (the adjudicator) who then decided which of the first two reports he/she most agrees with and this became the final radiological report. Following the radiological review, clinical data (including such information as presence of B-symptoms, biopsy or bone marrow aspirate result) and the radiological report were reviewed by an independent oncologist to determine the tumour response at that time-point. There was no adjudication process if the oncologist's assessment differed from that of the radiological assessment. All independent reviewers were blinded to patient's name, date of birth and investigational site.

All IRRC reviewers received specific training in the use of the 2007 IWG criteria and general requirements for independent readings. Each reviewer, radiology and oncology, completed a number of sample cases to ensure training had been effective. The performance of radiological reviewers was audited to check both intra-rater and inter-rater reliability. Intra-rater reliability was assessed by a process of 'secondary reviews', a random selection of a number of previously reported images was presented to the radiologist (who was blinded to this process) with independent comparison then made of the radiologist's two reports. Inter-rater reliability was assessed by review of the reports of the first 5 subjects reported by the radiologist with the reports checked against the 2007 IWG criteria. Significant deficiencies in the reports or discrepancies involving more than 30% of the secondary review scans prompted 'corrective actions' including communication of the review findings, phone/online/face-to-face discussion of and demonstration of the discrepancies.

Duration of response (DOR)

From the SAP, DOR is defined as the time from first response (CR or PR) to the date of initial objectively documented progression, as determined using the 2007 IWG criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored on the date of their last tumour assessment. Subjects who start subsequent therapy without a prior reported progression will be censored at the last tumour assessment prior to initiation of the subsequent anticancer therapy. Censoring criteria is shown in Table 22, below.

Table 22. Censoring criteria

Situation	Primary	Sensitivity
No progression per response criteria, no death and no subsequent anticancer therapy	Censored on the date of last tumour assessment	Censored on the date of last visit date
No progression per response criteria, no death and no subsequent anticancer therapy	Censored on the date of last tumour assessment prior or on the date of initiation of the subsequent anticancer therapy	Censored on the date of last visit prior or on the date of initiation of the subsequent anticancer therapy
Progression per response criteria without a subsequent anticancer therapy started	Event on the date of the first documented tumour progression per response criteria	Event on the date of the first document tumour progression per response criteria
Subsequent anticancer therapy started without a reported progression per response criteria	Censored on date of last tumour assessment prior or on the date of initiation of the subsequent anticancer therapy	Censored on date of last visit prior or on the date of initiation of the subsequent anticancer therapy
Death without progression per response criteria and without subsequent anticancer therapy started	Event on the date of death	Event on the date of death

Censoring scheme for primary analysis of DOR aligns with censoring scheme for PFS analysis. Last visit is defined as the date of last dosing, tumour, or lab assessment; whichever happens first.

7.1.8.3. Other endpoints

These included:

- Safety and tolerability
- Pharmacokinetics

- Samples will be collected to characterize pharmacokinetics of nivolumab and to explore exposure-safety and exposure-efficacy relationships.

· Immunogenicity

- Blood samples were collected and evaluated for the presence of antibodies to nivolumab (anti-drug antibodies (ADA)). The presence of neutralizing antibodies was also evaluated in ADA positive samples.

· Biomarkers, including PD-L1

- Biomarkers including programmed death-ligand 1 (PD-L1) and 9p24.1 alteration in Reed-Sternberg cells were measured in tumour tissue samples collected at Baseline (prior to first dose of study drug).
- Other biomarkers potentially associated with clinical endpoints will be measured by analysing tumour, bone marrow aspirates and blood samples. Biomarker endpoints include, but are not limited to, single-nucleotide polymorphisms (SNPs), proteins in tumour specimens and serum, and immune cell populations.

· Outcome research

- Health-related quality of life (HRQoL) will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire version 3. The EORTC QLQ-C30 is composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptoms (fatigue, nausea and vomiting, and pain) and a global health status/QOL scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).
- Subjects' overall health status will be assessed using the EuroQol Group's self-reported health status measure (EQ-5D-3L).

7.1.8.4. Safety

The safety analysis included all enrolled patients (Cohorts A, B and C). Safety assessments were based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation or dose modification, select AEs, immune-mediated AEs (IMAEs), and clinical laboratory assessments.

7.1.9. Randomisation and blinding methods

Randomisation: Not applicable. Patient eligibility was determined at screening according to the criteria for each cohort.

Blinding: Not applicable. This was an open label study. IRRC reviewers were blinded to patient identifying details such as name, DOB and investigational site.

7.1.10. Analysis populations

Within each cohort, the following populations were defined as:

· Enrolled subjects: All subjects

· Enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS.

· Treated subjects: All subjects who received at least one dose of nivolumab. This is the primary population for efficacy and safety.

· Response evaluable subjects: All treated subjects who have baseline and at least one on-study evaluable tumour measurement.

· Immunogenicity evaluable subjects: See Core SAP1 [not included here].

- PD-L1 tested subjects: All subjects who had a tumour tissue sample available for assessment of PD-L1 expression.
- PD-L1 evaluable subjects: All treated subjects with quantifiable baseline PD-L1 expression.
- Outcomes Research subjects: All treated subjects who have an assessment at Baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment (for EORTC QLQ-C30 and EQ-5D separately).
- Nivolumab subjects treated beyond progression: All subjects who received at least one dose of nivolumab after the date of initial progression per 2007 IS. VG criteria based on investigator assessment.
- Persistent CR subjects: All treated subjects in Cohort C who discontinue following a CR of 1 year duration.

7.1.11. Sample size

From the statistical analysis plan:

'The planned sample size for the whole study will be approximately 320 treated subjects, placed into three cohorts of subjects: brentuximab vedotin-naïve (n = 60; Cohort A), treatment with brentuximab vedotin after failure of ASCT (n = 60; Cohort B), and treatment with brentuximab vedotin at any timepoint (n = 200; Cohort C).

The sample size for Cohorts A and B was determined according to the ability to produce a CI which would exclude an ORR of 20%, which is not considered clinically relevant, and that would also provide sufficient information for a reliable understanding of the safety profile. Assuming the true ORR is 40%, each cohort has approximately 93% power to reject the null hypothesis that the true ORR is ≤ 20%, considering a 2-sided alpha of 5%.'

7.1.12. Statistical methods

Primary analysis will be performed separately for each cohort (that is, at separate time points) upon completion of a pre-specified amount of follow-up after last patient first treatment (LPFT). The ORR based on IRRC assessment will be summarized by binomial response rates and their corresponding two-sided 95% exact confidence intervals (CI) using the Clopper-Pearson method. The null hypothesis will be rejected if the 2-sided 95% CI lower bound is greater than 20%. DOR will be summarised for subjects who achieve PR or CR using the Kaplan-Meier product-limit method. Median values of DOR along with two-sided 95% CIs and range will also be calculated.

Pre-specified sub-groups for analysis of IRRC-assessed ORR are:

- Age (< 65; ≥ 65 and < 75; ≥ 75 and < 85; ≥ 85; ≥ 75; ≥ 65; < 30; ≥ 30 and < 45; ≥ 45 and < 60; ≥ 60)
- Region (US/Canada, Europe, Rest of the World)
- Gender (Male, Female)
- Race (white, black, Asian, and other)
- Smoking status (yes, no)
- ECOG (0, 1)
- B-symptoms at Baseline (absent, present)
- Time from the initial diagnosis to transplant (< 1 year; 1 ≤ 2 years; 2 ≤ 3 years; 3 ≤ 4 year; 4 ≤ 5 year; ≥ 5 year)
- Number of prior therapies (≤ 3; 4 to 6; ≥ 7) excluding preparative regimen

- Time from the most recent transplant to first subsequent treatment (< 6 months; 6 ≤ 12 months; ≥ 12 months)
- Categories including less than 5 subjects may be collapsed. Analyses of subgroups of less than 5 subjects may not be provided.

Sensitivity analyses:

- a summary of IRRC-assessed ORR based on response evaluable subjects instead of all treated subjects will also be presented.
- BOR will be cross-tabulated by assessment type (Investigator versus IRRC) and the Concordance Rate of Responders will be computed (defined as the frequency with which Investigator and IRRC agree on classification of a subject as responder/non-responder as a proportion of the total number of subjects assessed).

PFS (IRRC assessed) and OS analysis will be described using the Kaplan-Meier method.

7.1.13. Study Drug Exposure

All patients received at least one dose of nivolumab.

- *Cohort B*: The median number of doses administered was 17 (range 3 to 25); 76% received ≥ 90% of planned dose intensity.
- *Cohort A*: The median number of doses administered was 11 (range 1 to 24); 87% received ≥ 90% of planned dose intensity.
- *Cohort C*: The median number of doses administered was 6 (range 1 to 14); 86% received ≥ 90% of planned dose intensity.

7.1.14. Participant flow

Cohort B: 80 patients were treated.

At DBL

- 51/80 were continuing in treatment
- 29/80 had discontinued treatment
  - 13 stopped due to disease progression
  - 4 due to nivolumab toxicity
  - 2 at subject request
  - 8 for 'other reason'
  - 1 was lost to follow-up
  - 1 was not reported.

There were five patients not continuing in the study: 1 had died, 2 withdrew consent and 2 were lost to follow-up, and one patient whose status in the study was 'not reported'.

Participant flow for all cohorts at DBL is shown in Table 23 below.

Table 23. Participant flow, all Cohorts

	Cohort A	Cohort B	Cohort C	Cohort A+B+C
SUBJECTS ENROLLED				276
SUBJECTS NOT ENTERING THE TREATMENT PERIOD (%)				36 (13.0)
SUBJECTS ENTERING THE TREATMENT PERIOD	63	80	97	240
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	54 (85.7)	51 (63.8)	90 (92.8)	195 (81.3)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	9 (14.3)	29 (36.3)	7 (7.2)	45 (18.8)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)				
DISEASE PROGRESSION	4 (6.3)	13 (16.3)	3 (3.1)	20 (8.3)
STUDY DRUG TOXICITY	3 (4.8)	4 (5.0)	3 (3.1)	10 (4.2)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	2 (2.5)	1 (1.0)	3 (1.3)
LOST TO FOLLOW-UP	0	1 (1.3)	0	1 (0.4)
OTHER	2 (3.2)	8 (10.0)	0	10 (4.2)
NOT REPORTED	0	1 (1.3)	0	1 (0.4)
SUBJECTS CONTINUING IN THE STUDY (%) (A) (B)	61 (96.8)	74 (92.5)	94 (96.9)	229 (95.4)
SUBJECTS NOT CONTINUING IN THE STUDY (%) (B)	2 (3.2)	5 (6.3)	3 (3.1)	10 (4.2)
NOT REPORTED (%)	0	1 (1.3)	0	1 (0.4)
REASON FOR NOT CONTINUING IN THE STUDY (%)				
DEATH	1 (1.6)	1 (1.3)	3 (3.1)	5 (2.1)
SUBJECT WITHDREW CONSENT	1 (1.6)	2 (2.5)	0	3 (1.3)
LOST TO FOLLOW-UP	0	2 (2.5)	0	2 (0.8)
PERSISTENT CR SUBJECTS (%) (C)	N.A.	N.A.	0	0

Percentages based on subjects entering period or continuing study
(A) Includes subjects still on treatment and subjects off treatment continuing in the Follow-up period.
(B) Subject status at end of treatment.
(C) Treated subjects in Cohort C who discontinued treatment following a CR of 1 year duration.

7.1.15. Subsequent anti-tumour therapy

At the time of the interim analysis, 13 patients in Cohort B had received subsequent systemic anti-cancer therapy (16.3%): 10 subjects had systemic therapy and 6 subjects underwent SCT including allo-SCT (n = 5) and ASCT (n = 1) as shown in Table 24, below.

Table 24. Subsequent anti-tumour therapy

Patient number	BOR per IRRC	BOR per investigator	Time between last nivolumab dose and new treatment (months)	Subsequent anti-cancer therapy
1	CR	PR	1	Allo-SCT
2	PR	PR	1	Allo-SCT
3	SD	CR	1	Allo-SCT
4	PR	CR	0.5	Thiotepa + fludarabine + melphalan + allo-SCT
5	SD	CR		Thiotepa + cyclophosphamide + fludarabine + allo-SCT
6	SD	SD	0.5	Thiotepa + cyclophosphamide + fludarabine + Allo-SCT
7	PR	SD	1	Melphalan + fludarabine + ASCT
8	PD		1	Bendamustine
9	SD	SD	1	Gemcitabine + methylprednisolone
10	PR	PR	0.5	Gemcitabine Ipilimumab Gemcitabine + oxaliplatin

Patient number	BOR per IRRC	BOR per investigator	Time between last nivolumab dose and new treatment (months)	Subsequent anti-cancer therapy
11	PR	PR	2.5	Bleomycin + cyclophosphamide + etoposide+ procarbazine + vincristine + prednisolone
12	PR	SD	1.5	Everolimus
13	SD	SD	1	Mechlorethamine + procarbazine + vincristine + prednisolone
Cohort A				
1	?		7	Bendamustine
2	?		2	Brentuximab Vedotin
3	?		5	Brentuximab Vedotin
4	?		1	Brentuximab Vedotin

a) 3 treatment regimens over 6 month period; b) symbol '?' indicates a BOR for these patients was not provided.

Note: Actual patient identify numbers have been removed to maintain patient confidentiality. Numbers in the 'Patient number' column are used to indicate the information contained in each row relates to a single patient and patients are listed in no particular order.

7.1.15.1. SCT

In Cohort B, 6 patients elected to stop the study drug and proceeded to SCT (allo-SCT: n = 5, ASCT: n = 1). Of these patients, 4 had achieved CR or PR per investigator with nivolumab and 2 had maintained SD. Acute GVHD was reported in 3 subjects (Grade 1 or 2). According to the CSR, these events were '*considered moderate and acceptable as post allo-SCT events*'. All 6 subjects were alive at the time of the interim analysis.

Table 25. SCT after nivolumab treatment, Cohort B

BOR to Nivolumab Prior to SCT			Interval Between Last Nivolumab Dose and SCT Date (days)	
IRRC	Investigator	Type of SCT		GVHD
CR	PR	allo-SCT	41	Grade 1
SD	SD	allo-SCT	28	Grade 2
PR	PR	allo-SCT	37	Not reported
SD	CR	allo-SCT	31	Grade 1
PR	CR	allo-SCT	23	Not reported
PR	SD	ASCT	22	Not reported

Note: The sixth patient listed in the above table was reported as having been taken off study in order to receive allo-SCT; in addition the Table above does not include 1 subject who discontinued study treatment for a planned 'allo-transplant', however no allo-SCT was reported for this subject as of the DBL.

According to a table [not included here] of the SCS, there were no patients in Cohort A or C who had ceased nivolumab for subsequent SCT at the time of the interim analysis.

Comment: GVHD and other complications of allo-SCT following nivolumab treatment is discussed further in Section 8: Clinical Safety.

7.1.16. Major protocol violations/deviations

Two different types of protocol deviations were described in the interim CSR.

7.1.16.1. Significant protocol deviations

An appendix of the CSR listed *'significant deviations'* with these defined as study conduct that differed significantly from the protocol, including GCP noncompliance. From this listing, it appears that there were 65 significant protocol deviations, involving 37 patients, reported to the time of DBL for the interim report summarised in Table 26, below. The cohort to which each patient belonged was not included in the listing.

Table 26. Summary of protocol deviations from an appendix of the interim CSR

Type of protocol deviation	Report number	Comment
Eligibility	8	These appeared to be mainly related to the timing of the screening tests. In one patient, treatment was commenced despite positive HCV serology.
Incorrect timing of tumour assessments or scheduled scans	14	Little detail was provided regarding these.
Consent	2	One patient was provided with an incorrect version of the consent form, another was not provided with a language appropriate consent form.
Dose delivery	4	On 3 occasions the dose was administered over approximately 30 minutes instead of 60; on one occasion there was only 10 days between successive doses.
Failure to discontinue	1	Nivolumab treatment was continued despite a positive pregnancy test.
Administrative	23	These mainly related to the timing of central submission of data

Comment: The format CA209-205-xx-yyy is used for the patient ID number in this study, with xx representing a 2 digit number and yyy representing a 3 digit number. The evaluator notes that 27 of the 65 reported protocol deviations have the same xx number (-33-). If this xx number represents the investigational site, then one site is over represented in the listing of significant protocol deviations, with 27/65 reports and involving 19 patients. These protocol deviation reports included tumour assessments outside the protocol defined window (6), delayed notification of SAEs (2), administration of nivolumab over approximately 30 minutes instead of 60 minutes (3), delayed submission of local laboratory results (15) and use of an inappropriate language consent form (1). The number and range of protocol deviations at site 33 (if the evaluator's interpretation of the format of the patient ID

number is correct) raise concerns regarding study conduct at this site. See Question 18: Study conduct in Study CA209205 in Section 11, below.

7.1.16.2. Relevant protocol deviations

A table [not included here] of the interim CSR lists *'relevant protocol deviations'*. These were defined in the SAP as having the potential to affect the interpretability of study results and included:

- On treatment
  - Subjects without documented classical Hodgkin's lymphoma
  - Subjects without prior ASCT
  - Subjects with prior brentuximab vedotin treatment (Cohort A only)
  - Subjects without prior brentuximab vedotin treatment (Cohorts B and C only)
  - Subjects with prior treatment history of brentuximab vedotin administered before first ASCT (Cohort B only)
  - Subjects without either measurable disease at Baseline or FDG avid by PET
  - Subject with baseline ECOG > 1
- On Study:
  - Any concurrent antineoplastic therapy (that is, chemotherapy, immunotherapy, radiation therapy except for palliative radiation therapy, or standard or investigational agents for treatment of cancer).

According to this table there were 15 such deviations, involving 14 patients. All 14 patients did not meet the inclusion criteria of measurable disease. According to the CSR, two patients were in Cohort A, one was in Cohort B and 11 were in Cohort C. The other 'relevant protocol deviation' was that of a patient in cohort C who received concurrent anti-tumour therapy during treatment with nivolumab. The CSR concluded that these protocol deviations would not affect the interpretability of study results as *'the no measurable disease/FDG-avid lesion deviations in Cohorts A and C do not affect study results reported in this interim CSR, since efficacy analysis in these Cohorts were not performed.'*

Comment: The absence of measurable disease at Baseline would affect the assessment of tumour response for those patients and, therefore, the efficacy analysis. The efficacy analysis for Cohort B is a major component of this interim report and submission. Inclusion of one patient who did not meet enrolment criteria for measurable/active disease could potentially affect the results of this analysis.
See Question 20: Inclusion of patients without measurable disease in Study CA209205 in Section 11, below.

The evaluator also notes that of these 14 patients, one appears to have been enrolled at presumed site 33 (enrolled in Cohort C) and that 7 were enrolled from presumed site 35 (all in Cohort C). The number of patients without measurable disease enrolled at one site raises concerns regarding study conduct at that site. See Question 18: Study conduct in Study CA209205 in Section 11, below.

7.1.17. Baseline data

In Cohort B (n = 80):

- The median age was 37 years. There were 3 subjects (3.8%) aged 65 years or older. The majority of subjects were white (88.8%) and male (63.8%).
- All subjects had a baseline ECOG PS of 0 or 1 with 52.5% having an ECOG PS of 1.
- The majority of the subjects had Stage IV disease at study entry (67.5%).

- Extra lymphatic involvement and bone marrow involvement at Baseline were reported in 45.0% and 10.0% of the Cohort B subjects, respectively.
- The median time from initial diagnosis to the first dose of nivolumab was 6.2 years while the median time from the most recent transplant to the fast dose of nivolumab was 3.4 years.
- The most common sites of lesions were lymph nodes (92.5%) and lung (27.5%). The median sum of products of diameters (mm^2) was 1662.5 (range 160 to 16,943).
- 18 subjects (22.5%) had B-symptoms at Baseline.

Of note is that 71/80 patients were Caucasian, with 4 African Americans, 1 Asian and 4 were of 'other' race.

In Cohorts A + B + C:

- The median age was 34 years. There were 7 subjects (2.9%) aged 65 years or older. The majority of subjects were white (86.7%) and male (58.8%).
- All subjects had a baseline ECOG PS of 0 or 1 with 54.6% having an ECOG PS of 0.
- The majority of the subjects had Stage IV disease at study entry (56.7%).
- Extra lymphatic involvement and bone marrow involvement at Baseline were reported in 41.3% and 7.5% of subjects, respectively.
- The median time from initial diagnosis to the first dose of nivolumab was 4.4 years while the median time from the most recent transplant to the first dose of nivolumab was 2.0 years.

7.1.18. Results for the primary efficacy outcome

7.1.18.1. Cohort B: Objective response rate (ORR) per IRRC

At time of analysis, median duration of follow-up for Cohort B was 8.9 months (range 1.9, 11.7).

- ORR per IRRC = 53/80, 66.3% (95% CI 54.8, 76.4)
  - No with CR = 7
  - No with PR = 46
- 31/53 responders were continuing on treatment at time of analysis
- 33/53 were still in response at last assessment; 20/33 had been in response for 4 months or longer.

Comment: An updated analysis of efficacy (DBL of April 2016 compared to October 2015) is provided in the sponsor's response to Question 16: Updated results from Study CA209039 and Study CA209205 in Section 12, below.

Additional detail regarding the breakdown of responses is shown Table 27, below.

Table 27. BOR per IRRC, Cohort B, all treated subjects

	Cohort B N = 80
BEST OVERALL RESPONSE (1):	
COMPLETE REMISSION (CR)	7 (8.8)
(95% CI)	(3.6, 17.2)
PARTIAL REMISSION (PR)	46 (57.5)
(95% CI)	(45.9, 68.5)
STABLE DISEASE (SD)	18 (22.5)
RELAPSED OR PROGRESSIVE DISEASE (PD)	6 (7.5)
UNABLE TO DETERMINE (UTD)	3 (3.8)
NO BASELINE CT SCAN AVAILABLE	0
NOT ELIGIBLE FOR RADIOLOGY REVIEW: OTHER REASON	0
NO EVIDENCE OF DISEASE	0
NO POST-BASELINE TUMOR ASSESSMENT AVAILABLE BEFORE OR ON THE DAY OF SUBSEQUENT THERAPY (IF ANY)	2 (2.5)
ALL POST-BASELINE TUMOR ASSESSMENTS BEFORE OR ON THE DAY OF SUBSEQUENT THERAPY (IF ANY) ARE UNKNOWN	1 (1.3)
OBJECTIVE RESPONSE RATE (2)	53/80 (66.3%)
(95% CI)	(54.8, 76.4)

1) Per revised International Working Group Criterial for Malignant Lymphoma (2007); 2) CR + PR, confidence interval based on the Clopper and Pearson method.

The BOR could not be determined in 3 subjects, as shown in Table 27, above.

Comment: This did not include one patient for whom there was no measurable disease at Baseline.

Sensitivity analyses for ORR per IRRC

IRRC-assessed ORR in response evaluable subjects (n = 74) was 71.6% (95% CI: 59.9, 81.5).

The definition of 'Response evaluable subjects' is those subjects with:

1. a BOR of CR, PR, SD or PD
2. target lesion(s) assessed at Baseline; and
3. at least 1 on-study time-point with all baseline target lesion(s) assessed.

Comment: There were 6/80 patients who apparently did not meet the definition of 'Response evaluable subjects'. These 6 patients, and the way in which each patient did not meet the criteria for 'response evaluable subject', were not explicitly described in the CSR. See Question 21: Response evaluable patients in Study CA209205, in Section 11, below.

Sub-group analyses for ORR per IRRC

Analyses of a number of pre-specified subgroups were conducted. These subgroups included age, gender, race, region, smoking status, B-symptoms at initial diagnosis, baseline ECOG performance status, time from initial diagnosis to first transplant, time from recent transplant to first subsequent therapy, and number of prior lines of cancer therapy (see Section 7.1.12: Statistical Methods, above). For all sub-groups, the results were consistent with the overall group, although for some groups with small numbers, the confidence intervals were very wide.

7.1.19. Results for the secondary efficacy outcomes

7.1.19.1. Cohort B: Time to Response (TTR) per IRRC

- The median TTR was 2.1 months (range 1.6 months to 5.7 months)
  - 31 of the 53 (58.5%) responders achieved their response by the time of first scan (9 weeks), and all of the responses were achieved within 6 months of treatment initiation.

- The median time to CR was 4.44 months (range 3.3 months to 6.9 months)
- The median time to PR was 2.10 months (range 1.6 months to 5.7 months).

7.1.19.2. Cohort B: Duration of Response (DOR) per IRRC

Comment: As noted in the interim CSR, estimates of the median duration of response are immature due to censoring with 31/53 responders per IRRC still on treatment and censored prior to the median as shown in Table 28, below (see Section 7.1.8.2: Duration of response (DOR) above for definition and censoring rules).

Table 28. Duration of Response per IRRC and per Investigator, Cohort B, All responders

	Cohort B Responders	
	IRRC N=53	Investigator N=58
DOR (Months)		
Min, Max[a]	0.0+, 9.5+	0.0+, 9.5+
Median (95% CI)[b]	7.79 (6.64, N.A.)	9.10 (6.74, N.A.)
N Event/N Response (%)	11/53 (20.8)	9/58 (15.5)
Duration of CR (Months)[c]		
Min, Max[a]	0.7+, 4.6	0.0+, 8.7
Median (95% CI)[b]	4.63 (N.A., N.A.)	8.74 (N.A., N.A.)
N Event/N Response (%)	1/7 (14.3)	1/22 (4.5)
Duration of PR (Months)[d]		
Min, Max[a]	0.0+, 9.5+	0.0+, 7.8
Median (95% CI)[b]	7.79 (6.64, N.A.)	7.79 (6.74, 7.79)
N Event/N Response (%)	10/46 (21.7)	8/36 (22.2)
Number of Subjects with DOR of at least (%)		
3 Months	38 (71.7)	37 (63.8)
6 Months	14 (26.4)	13 (22.4)
Subjects with Ongoing Response[e]	33/53 (62.3)	39/58 (67.2)
Subjects with Ongoing Response of Duration of ≥4 Months[e]	20/53 (37.7)	21/58 (36.2)
Subjects with Ongoing Response of Duration of ≥6 Months[e]	9/53 (17.0)	10/58 (17.2)

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete remission; DOR = duration of response; IRRC = Independent Radiologic Review Committee; N.A. = not available, minimum follow-up not reached; PR = partial response.

[a] Symbol + indicates a censored value

[b] Median computed using Kaplan-Meier method

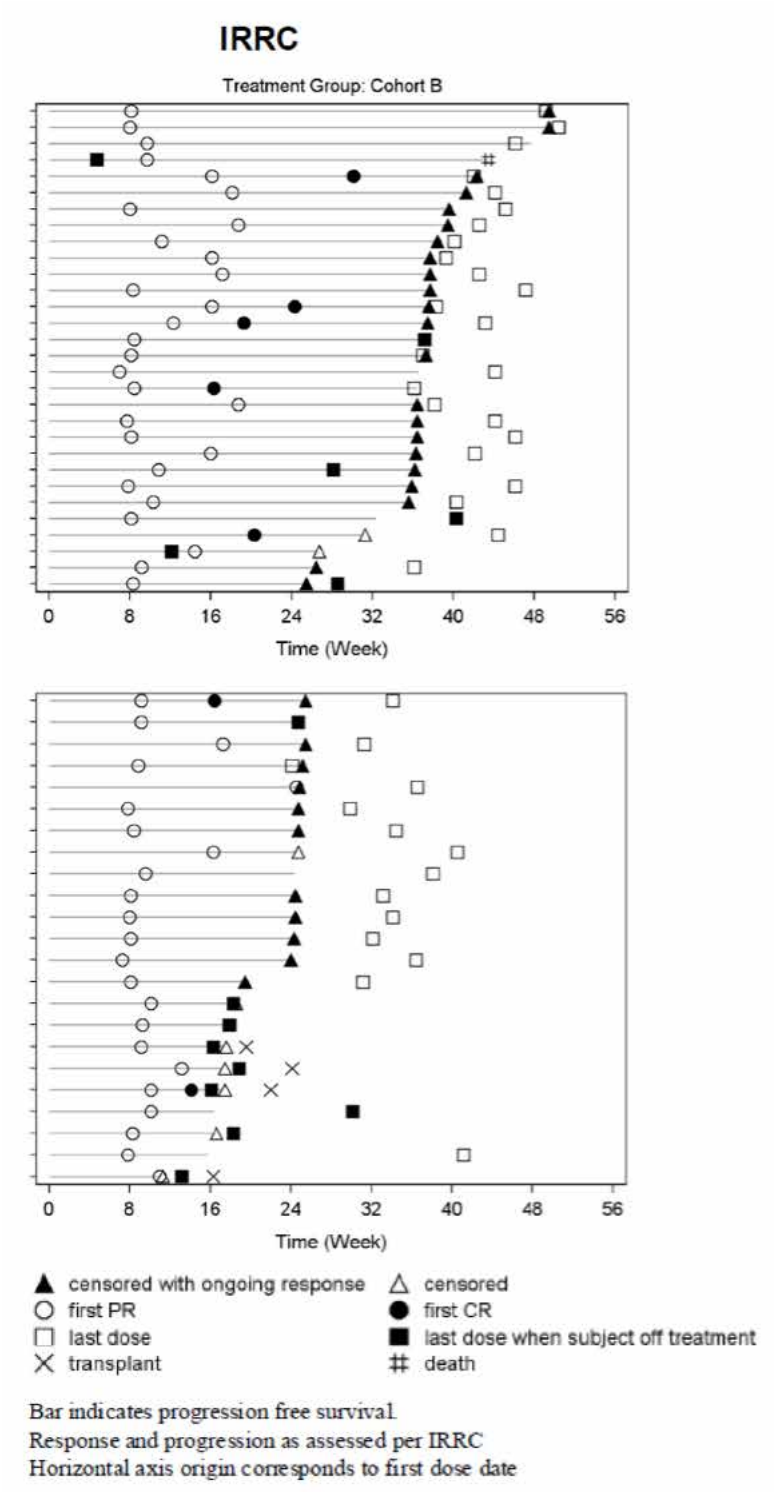
[c] Subjects with BOR of CR

[d] Subjects with BOR of PR

[e] Subjects with Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis, and excludes responders censored prior to 14 weeks of the clinical data cutoff date.

Event charts of Time to Response and Duration of Response for Cohort B were provided in the interim CSR (see Figure 16 below).

Figure 16. Event chart for time to response and duration of response, Cohort B, All responders as assessed by IRRC



Note: Each horizontal bar denotes one study subject

Comment: From the event chart, it seems that most of the patients who were censored for the analysis of DOR, were censored at the time of the last tumour assessment due to the situation of '*No progression per response criteria, no death and no subsequent anticancer therapy*' and that most of these patients have been treated for 24 weeks or longer. This suggests that the median DOR as shown may be an underestimate of the DOR that may be reported with more prolonged follow-up – the sponsor is requested to provide updated efficacy results for DOR and other outcome measures.

See Question 16: Updated results from Study CA209039 and Study CA209205, in Section 11, below.

Sensitivity analysis for DOR per IRRC

For this sensitivity analysis, subjects who remained alive and did not progress were censored on the last visit date prior to initiation of subsequent cancer therapy. Last visit was defined as the last date of dosing, evaluable tumour assessment or lab assessment, whichever occurred last. The censoring scheme for this analysis is shown in Section 7.1.8.2, above. The results were immature with the median DOR not reached for the group overall or the CR or PR group and are shown in Table 29, below.

Table 29. Duration of response per IRRC, sensitivity analysis, Cohort B, all responders

	Cohort B responders
DOR (months)	
Min, Max[1]	0.5+, 9.8+
Median (95% CI)[2]	N.A. (6.83, N.A.)
N Event/N Response (%)	11/53 (20.8)
Note: 1) + indicates a censored value; 2) Median computed using Kaplan-Meier method	

Comment: In both the primary analysis of DOR and in the sensitivity analysis, patients who had not progressed or died but who had received subsequent anti-cancer therapy were censored. Of the 13 patients who received subsequent anti-tumour therapy, 9 achieved BOR of CR or PR. The sponsor is asked to repeat the sensitivity analysis with these patients counted as having an event instead of being censored, using updated data. See Question 24: Sensitivity analysis of DOR in Study CA209205 in Section 11, below.

7.1.19.3. Cohort B: ORR and DOR per investigator

The results per investigator are shown in Table 30 below, together with the results per IRRC.

Table 30. ORR and DOR per IRRC and investigator

Efficacy parameter	Result per IRRC	Result per Investigator
	All patients (n = 80)	All patients (n = 80)
ORR (CR + PR/23)	66.3% (95% CI 54.8, 76.4)	72.5% (95% CI 61.4, 81.9)
No with CR + PR	53	58
No with CR	7	22
No with PR	46	36
No with SD	18	18
No with PD or relapse	6	3
Unable to determine	3	1
DOR		
Events*	11/53	9/58

Efficacy parameter	Result per IRRC	Result per Investigator
	All patients (n = 80)	All patients (n = 80)
Median (95%CI) (months)	7.79 (6.64, NA)	9.10 (6.74, NA)
Range (months)	0.0+, 9.5+	0.0+, 9.5+
Note: a) Events were progression or death. For responders who did not have reported progression or death date, DOR was censored at the last tumour assessment date and is denoted by a + symbol.		

The concordance rate between IRRC and investigator assessments was 76.3% for ORR and 53.8% for BOR (see Table 31, below).

Table 31. Concordance rate, IRRC and investigators

	Number of Subjects (%)			
	Cohort B N = 80			
	IRRC ASSESSMENT			
	RESPONDER	NON-RESPONDER	UTD	NOT REPORTED
INVESTIGATOR ASSESSMENT				
RESPONDER	47 (58.8)	11 (13.8)	0	0
NON-RESPONDER	6 (7.5)	13 (16.3)	2 (2.5)	0
UTD	0	0	1 (1.3)	0
NOT REPORTED	0	0	0	0
CONCORDANCE RATE OF RESPONDERS (1):		76.3 %		

Responder: Subject with PR/CR. UTD : Unable to Determine
(1) Quantifies the frequency with which the Investigator and IRRC agreed on classification of a subject as responder/non responder/UTD as a proportion of the total number of subjects assessed by both Investigator and IRRC.
Program Source: /projects/bms220633/stats/primary/prog/tables/rt-ef-resp-concord-b.sas 13JAN2016:06:11:48

Comment: There is a small difference in the overall number of responders, with 53 responders per IRRC and 58 responders per investigator. However, there is considerable difference in the categorisation of responders, with 7 patients with CR per IRRC compared to 22 per investigator. According to the interim CSR this discordance in CRs *was due mainly to different interpretation (positive or negative) of FDG-PET scans required for confirmation of a CR*. The following additional information was provided:

- 3 subjects were CR by both IRRC and investigator.
- 4 subjects were CR by IRRC but non-CR (3 PR and 1 SD) by investigators
  - in these patients, there were conflicting assessments of the PET scan(s) by the two IRRC radiologists, with adjudication by the third radiologist required.
- 19 subjects were CRs by investigators but non-CRs (14 PRs, 3 SDs, and 2 PDs) by IRRC.

Descriptions of the assessments of the radiologic scans were provided in tables [not included here]. The difficulty of determining radiological response in some patients is shown by the number of assessments in which the third radiologist was required to adjudicate. This occurred in 13/23 of the patients in whom the IRRC and investigator assessments were discordant.

7.1.20. Results for other efficacy outcomes

7.1.20.1. Cohort B: PFS by IRRC

At median follow-up of 8.9 months and with 24 events (23 progression and 1 death), the median PFS per IRRC was estimated at 9.99 months (95% CI: 8.41, NA).

There were 56 (out of 80) patients censored in the analysis:

- receiving subsequent anti-cancer therapy (n = 9)
- still on-treatment (n = 39)
- progression free in follow-up (n = 4)
- off-study due to consent withdrawal (n = 1)
- No baseline tumour assessment/no death (n = 1)
- No on-study tumour assessment/no death (n = 2).

PFS results were similar between IRRC and investigator assessments (median PFS: 10.0 months versus 10.9 months; 6-month PFS rate: 76.9% versus 82.6%).

Comment: The median PFS is appropriately described by the sponsor as 'unstable' due to the number of patients censored. The duration of therapy of the 56 patients still on treatment compared to the 24 included in the PFS analysis is not provided. No conclusions can be drawn as to whether the PFS reported is likely to be a minimum PFS.

7.1.20.2. Cohort B: Overall Survival

With a median follow-up time for OS of 8.9 months (range 1.9, 11.7) and 3 death events in Cohort B, the median OS was not reached.

Of the 77 subjects who were censored for OS, 51 (63.8%) were still on treatment, 21 (26.3%) were in follow-up, and 5 (6.3%) were off study.

7.1.20.3. Cohort B: Efficacy by prior response to brentuximab vedotin

Best overall response to nivolumab treatment by prior response to brentuximab as documented in subject's medical record was examined on a post-hoc basis.

Of the 80 subjects in Study CA209205 Cohort B, 43 (53.8%) had no response (SD or PD/relapse) to prior brentuximab vedotin treatment, 23 had response of CR (n = 6) or PR (n = 17) and in 14 the response could not be determined.

With nivolumab treatment:

- Of the 6 patients with best response of CR to prior brentuximab vedotin, 4 had PR and 2 had SD per IRRC with nivolumab.
- Of the 17 patients with best response of PR to prior brentuximab vedotin, 1 had CR, 8 had PR, 7 had SD and 1 had PD per IRRC with nivolumab.
- Of the 9 patients with best response of SD to prior brentuximab vedotin, 2 had CR, 4 had PR, 1 had SD and 1 had PD per IRRC and 1 was undeterminable with nivolumab.
- Of the 34 patients with best response of relapse or PD to prior brentuximab vedotin, 3 had CR, 22 had PR, 5 had SD and 3 had PD per IRRC and 1 was undeterminable with nivolumab.
- Of the 14 patients with undeterminable response to prior brentuximab vedotin, 1 had CR, 8 had PR, 3 had SD and 1 had PD per IRRC and 1 was undeterminable with nivolumab.

Comment: This exploratory post-hoc analysis suggests no relationship between prior response to brentuximab vedotin and subsequent response to nivolumab.

7.1.20.4. Cohort B: Subjects treated beyond investigator-assessed progression

There were 9 subjects who had progressed, according to the 2007 IWG criteria as assessed by the investigators, who were considered eligible per protocol to receive continued nivolumab therapy. The number of doses received beyond progression ranged from 1 to 14 and the duration of treatment beyond progression ranged from 0.5 to 6.4+ months.

Among these 9 subjects treated beyond progression, 6 maintained tumour reduction in target lesion. Of these 6 subjects, 5 maintained reduced tumour burden after the appearance of new lesions and the other had new lesion at the data cut-off.

Comment: There were 23 patients who had progression events. Of these, 9 continued on treatment. Interpreting the benefit, or otherwise, of treatment beyond progression requires more information on how these 9 patients may have differed from the other 14 patients. See Question 22: Treatment beyond progression in Study CA209205 in Section 11, below.

7.1.21. Results for other outcome measures

7.1.21.1. Cohort B: Objective Response per IRRC and PD-L1 expression

Objective response per IRRC with nivolumab in Cohort B subjects was observed regardless of baseline PD-L1 expression status:

- In subjects with PD-L1 ≥ 1% expression, the ORR was 66.7%. Among the 38 subjects with a BOR, 4 had a CR and 34 had a PR.
- In subjects with PD-L1 < 1% expression, the ORR was 83.3%. All 5 subjects had a PR.
- In subjects without quantifiable PD-L1, the ORR was 58.8%. Among the 10 subjects with a BOR, 3 had a CR and 7 had a PR.

7.1.21.2. Cohort B: Resolution of B-symptoms

There were 18/80 patients with B symptoms at Baseline. Of these, 16/18 had resolution of these symptoms.

7.1.21.3. Cohort B: Quality of Life Measures

Cancer-related Quality of Life, EORTC-QLQ-30

The EORTC-QLQ-C30 questionnaire version 3 was used to assess HRQoL. The EORTC-QLQC30 is made up of 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), a global health status/QoL scale, 3 symptom scales (fatigue, nausea, and pain), and 6 individual items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). A score difference of 10 was used as an estimate of the minimal important difference (MID) for all subscales of the EORTC-QLQ C30, including the symptom scales.

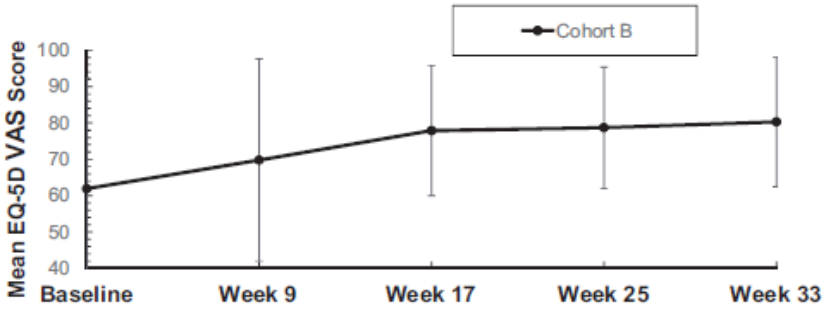
The rate of questionnaire completion at Baseline was 93.8% and remained greater than 80% for each visit for those subjects that were still participating in the study, up to visit at Week 33. There are only small numbers of completed questionnaires post-Week 33 (9/16 patients) and at the follow-up visits (8/21 patients at follow-up Visit 1 and 1/7 patients at follow-up Visit 2).

Generic Health Status - EQ-5D VAS

The EQ-5D VAS elicits subjects' ratings of their health status on a 0 to 100 scale with 0 being the worst imaginable health state and 100 being the best imaginable health state. The MID for the EQ-5D VAS has been estimated to be 7 points. As with the EORTC-QLQ-30, there were very small numbers of questionnaires completed after Week 33 (n = 8) and the two follow-up visits (n = 7 and n = 1).

The baseline score for the EQ-5D VAS for the Cohort B subjects was 61.9 (SD 30.5) (see Figure 17, below). The average EQ-5D VAS score increased over time and exceeded the average baseline score by more than the 7-point MID from Week 9 through Week 33.

Figure 17. Mean EQ-5D VAS Score at each assessment



n	76	62	60	51	44
Cohort B, score (SD)	61.9 (30.47)	69.8 (27.82)	77.9 (17.90)	78.7 (16.72)	80.3 (17.81)

Abbreviations: SD = standard deviation; VAS = visual analog scale

Comment: Interpretation of the EORTC-QLQ-C30 results as provided in the interim CSR is difficult as the table of results is spread over 180 pages. According to the Summary of Clinical Efficacy: '*improvements from baseline were observed for: role function at Week 9 (mean change = 10.7, SD 9.0), social function at Week 33 (mean change = 10.6, SD 23.5), and insomnia at Week 33 (mean change = -12.2, SD 25.6). No clinically meaningful deterioration was observed in any of the EORTC QLQ-C30'.* The results for both QoL measures are consistent and would suggest that QoL in most patients, according to these measures, is not worsened during the first 33 weeks of nivolumab treatment.

7.2. Study CA209039

7.2.1. Study summary

The interim CSR reports efficacy results for a single sub-group from the study: 23 patients who had relapsed/refractory classical HL and who received nivolumab monotherapy at 3 mg/kg Q2W. A summary for this study is given in Table 32, below.

Table 32. Study CA209039 Summary

Study CA209039 Summary	
The interim study report describes the results of 23 patients who had classical HL and who received nivolumab monotherapy at 3 mg/kg Q2W. Of the 23 patients, 15 had received both prior ASCT and brentuximab vedotin as salvage therapy. The interim analysis of the cHL group was performed to support a regulatory application. Results were presented for the 15 ASCT-Bren Failed group, the 8 Other cHL group and the 23 all cHL group.	
Study identifier	CA209039
Study title	A Phase I dose escalation study to investigate the safety, pharmacokinetics, immunoregulatory activity, and preliminary antitumor activity of anti-programmed-death 1 (PD-1) antibody (nivolumab, BMS-936558) and the combinations of nivolumab and ipilimumab or nivolumab and lirilumab in subjects with relapsed or refractory haematologic malignancy.
Related publication	Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015;372:311-9.

Study CA209039 Summary	
	Note: the date for this interim analysis was 16 June 2014.
Design	Phase I, open label, multicentre, dose escalation, and multidose study of nivolumab monotherapy and/or nivolumab in combination with ipilimumab or lirilumab in subjects with relapsed/refractory haematologic malignancy (including multiple myeloma, non-Hodgkin lymphoma, Hodgkin lymphoma and T cell lymphoma), with expansion cohorts in selected haematologic malignancies including HL.
Patient group	Subjects with relapsed/refractory haematologic malignancy. All Hodgkin Lymphoma subjects who enrolled in the nivolumab monotherapy cohort (n = 23) were treated with 3 mg/kg and had classical HL.
Dates	For the 23 patients reported in the interim CSR, enrolment commenced 21 December 2012 and ceased on 11 Nov 2013 with the last patient visit on 19 June 2015. Database lock for this interim report was 11 August 2015. The report is dated 15 January 2016.
Location(s)	23 enrolled subjects with cHL were treated at 7 sites in the United States
Main inclusion criteria	Inclusion criteria for HL patients were: histologically confirmed evidence of relapsed or refractory Hodgkin's lymphoma with at least one lesion measuring more than 1.5 cm, ECOG performance-status score of 0 or 1, previous treatment with at least one chemotherapy regimen, and no autologous stem-cell transplantation within the previous 100 days
Main exclusion criteria	Prior organ allograft or allo-SCT transplant, autoimmune disorders, concomitant second cancer, CNS lymphoma.
Randomisation and blinding	Not applicable.
Study treatments	Nivolumab 3 mg/kg with second dose given after three weeks and then every 2 weeks subsequently for up to 2 years or until confirmed complete remission (CR) per investigator, confirmed progressive disease (PD), or unacceptable toxicity.
Anti-tumour activity measures	The primary efficacy end-point of nivolumab monotherapy for cHL subjects was measured by investigator-assessed ORR using the 1999 IWG Response Criteria for Lymphomas. ORR was defined as the total number of subjects whose BOR is either a CR or PR divided by the total number of treated subjects. Other efficacy end-points were investigator-assessed and IRRC-assessed measures of ORR, CRR, PRR, mDOR (all, CR and PR), median time to response (all, CR and PR), PFSR, OS.
Other measures	Biomarker assessments including PD-L1, Immunogenicity of nivolumab; Safety and tolerability.

Study CA209039 Summary	
No of subjects and participant flow	23 patients with cHL received nivolumab monotherapy at 3mg/kg every 2 weeks. At the time of DBL for these 23 patients · 3 subjects were continuing with study drug treatment · 20 patients had discontinued study drug treatment for the following reasons: – 6 patients due to disease progression – 2 patients due to study drug toxicity (pancreatitis and MDS) – 5 at their own request or for 'other reason' so as to proceed to alloSCT (4) or ASCT (1) – of these, one patient had achieved CR – one patient at own request due to muscular/joint pain – 4 patients had achieved confirmed CR – 2 patients had completed 2 years of therapy. Outcomes at the time of DBL lock were: 3 continued in study drug treatment, 13 were off study therapy and in follow-up, 5 had died and 2 were lost to follow-up. Of the 15 ASCT-Bren Failed group: · 2 subjects were continuing with study drug treatment · 13 patients had discontinued study drug treatment for the following reasons: – 5 patients due to disease progression – 2 patients due to study drug toxicity (pancreatitis and MDS) – 3 at their own request or for 'other reason' – 2 patients had achieved confirmed CR per investigator – 1 patient had completed 2 years of therapy.
Study therapy exposure	All 23 cHL subjects received at least 1 dose of nivolumab. The median number of cycles was 18 (range 6 to 48); 78% received ≥ 90% of planned doses. The KM estimate of median treatment duration was 8.2 months (95% CI: 5.29, 15.87). The median number of doses for the 15 ASCT-Bren Failed group was 24 (range 6 to 48); 73% received ≥ 90% of planned doses. The KM estimate of median treatment duration was 12.1 months (95% CI: 3.88, 19.58).
Duration of follow-up	At the time of DBL, the median duration of follow-up for all 23 cHL subjects was 23.3 months (Min, Max: 7.3 to 27.8).
Results, demographics	20/23 patients were White; 12/23 were male; median age was 35 years (range 20 to 54); all were extensively pretreated with median of 5 prior treatments (range 2-15); 18 patients had received ASCT and 18 patients had received brentuximab vedotin (15 of whom had received ASCT prior to brentuximab vedotin). The ECOG PS was 0 for 11 patients and 1 for 12 patients. Of the 15 patients who had received brentuximab vedotin treatment as a salvage therapy after failure of ASCT ('ASCT-Bren Failed' group), 12/15 were White, the median age was 40 years (range 20-54) and around half were male. The ECOG PS was 0 for 7 patients and 1 for 8 patients.
Subsequent cancer therapy	A total of 12 cHL subjects reported subsequent cancer therapy: 8 were from the cHL ASCT-Bren Failed group.

<table>
<tr><th colspan="2">Study CA209039 Summary</th></tr>
<tr><td></td><td>There were 6 patients who ceased nivolumab treatment to undergo SCT (5 allo-SCT and one ASCT). These patients had achieved the BOR per investigator of CR (n = 1), PR (n = 5)</td></tr>
<tr><td>Anti-tumour activity</td><td>ORR (after median follow-up of 23.3 months)
<table>
<tr><th></th><th colspan="2">Result Per IRRC</th><th colspan="2">Result Per investigator</th></tr>
<tr><th>Efficacy parameter</th><th>All patients (n = 23)</th><th>ASCT-Bren Failed Group (n = 15)</th><th>All patients (n = 23)</th><th>ASCT-Bren Failed Group (n = 15)</th></tr>
<tr><td>ORR (CR+PR/total)</td><td>61%</td><td>60%</td><td>87%</td><td>87%</td></tr>
<tr><td>No with CR</td><td>3</td><td>0</td><td>5</td><td>2</td></tr>
<tr><td>No with PR</td><td>11</td><td>9</td><td>15</td><td>11</td></tr>
<tr><td>No with SD</td><td>7</td><td>5</td><td>3</td><td>2</td></tr>
</table>
Duration of Response
KM estimate of median duration of response per IRRC
· 12 months (95% CI 1.8, NA) for the ASCT-Bren Failed Group
· Not reached for all cHL subjects.</td></tr>
<tr><td>Secondary outcomes</td><td>PFS
Based on the IRRC assessment of PFS, the KM estimate of median PFS for the ASCT-Bren Failed group was 12.7 months (95% CI, 5.91, N.A) and not reached for all cHL subjects.
OS
At the time of database lock for this interim report, with median follow-up of 23 months (range 7-28 months), 5 patients had died (21.7%), with 4 of these patients in the ASCT-Bren Failed group (4/15, 26.7%). The estimated median OS was not reached for cHL all subjects and the subgroup ASCT-Bren Failed group</td></tr>
<tr><td colspan="2">DOR: duration of response; IRRC: Independent radiologic review committee; IWG: International Working Group; ORR: objective response rate; OS: overall survival; OS: overall survival; PFS: progression-free survival</td></tr>
</table>

7.2.2. Study objectives

Table 33. Study CA209039 Objectives

Primary objective	To establish the dose limiting toxicities, maximum tolerated dose and recommended Phase II dose for nivolumab, up to a maximum dose of 3 mg/kg administered every 2 weeks to subjects with relapsed/refractory haematologic malignancy.
Secondary	· To characterise the pharmacokinetics of nivolumab in subjects with

objectives	relapsed/refractory haematologic malignancy · To assess the preliminary anti-tumour activity of various dose levels of nivolumab in subjects with relapsed/refractory haematologic malignancy · To characterise the immunogenicity of nivolumab in subjects with relapsed/refractory haematologic malignancy · To assess the potential association between anti-programmed-death 1 (PD-L1) expression on tumour cells as measured by immunohistochemistry and clinical efficacy measures.
Exploratory objectives	· To investigate the pharmacodynamic effects of nivolumab on selected markers of immune modulation in peripheral blood and tumour samples · To investigate the potential association between selected biomarker measures and clinical efficacy measures · To assess the overall survival up to five years for the monotherapy nivolumab

Comment: Only the results for the sub-group of 23 patients with cHL who received nivolumab monotherapy at 3 mg/kg every 2 weeks were reported in the interim CSR. No information was provided regarding the dose escalation phase of the study. The related publication by Ansell et al also describes the results for just these 23 patients although it does provide some additional information that: '*In the dose-escalation cohort, patients with relapsed or refractory haematologic cancers were treated with nivolumab at a dose of 1 mg per kilogram of body weight, with escalation of the dose to 3 mg per kilogram. Since the maximum tolerated dose was not reached, a dose of 3 mg per kilogram was chosen for the expansion cohorts.'* See Question 17: Dose escalation phase of Study CA209039 in Section 11, below.

7.2.3. Good Clinical Practice

The interim CSR states: '*This study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)'* and that, prior to subject enrolment, confirmation that investigator/study staff had completed GCP training was required.

7.2.3.1. Site training

Before study initiation, site initiation visits were conducted with training provided to investigational staff with regard to background information on study drug and administration, study design, objectives, inclusion/exclusion criteria, informed consent, AE/SAE reporting procedures and requirements, study procedures and logistics including use of vendors, enrolment of women of childbearing potential, investigator responsibilities and CRF completion prior to subject enrolment.

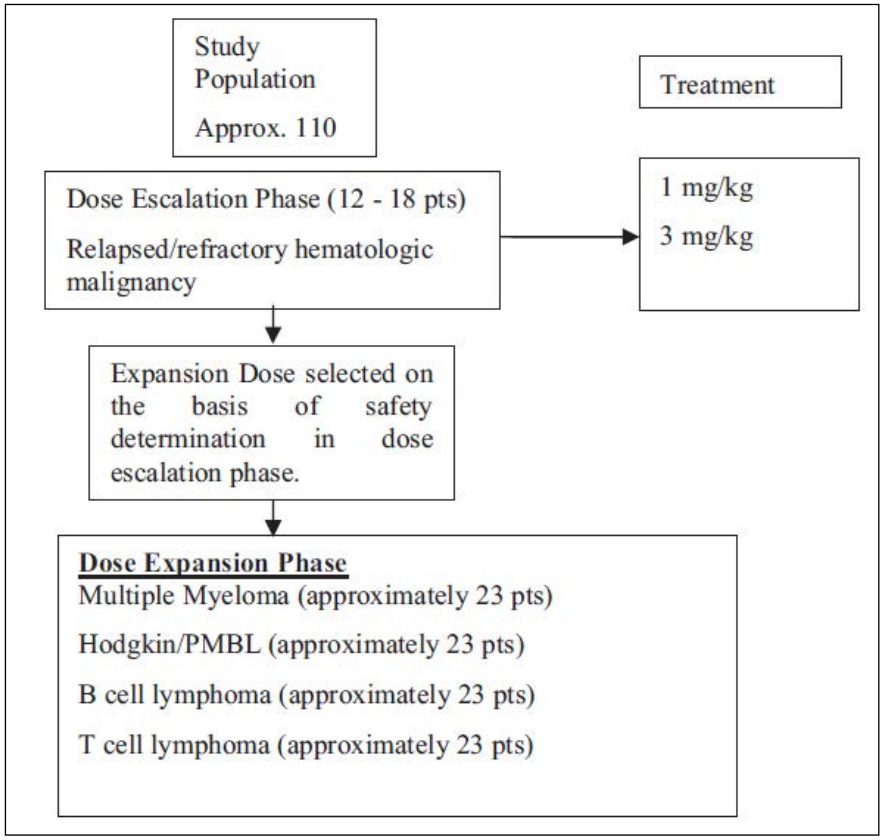
7.2.4. Study design

This was a Phase I, open label, multicentre, dose escalation, and multidose study of nivolumab monotherapy and/or nivolumab in combination with ipilimumab or lirilumab in subjects with relapsed/refractory haematologic malignancy, with expansion cohorts in selected haematologic malignancies including HL.

Figure 18, below, gives the study design for nivolumab monotherapy. The nivolumab monotherapy portion of the study included the dose escalation phase (12 to 18 subjects with relapsed/refractory haematologic malignancy treated with nivolumab 1 mg/kg and 3 mg/kg) followed by 4 expansion cohorts studying different types of haematologic malignancy (multiple myeloma, Hodgkin lymphoma, B cell lymphoma, and T cell lymphoma, n = 23 in each cohort). While this study allowed enrolment for any type of Hodgkin lymphoma including NLPHD, all

Hodgkin subjects who enrolled in the nivolumab monotherapy cohort (n = 23) were treated with 3 mg/kg and had cHL.

Figure 18. Study design for nivolumab monotherapy



7.2.4.1. Dose evaluation

From the study protocol: A 6 + 3 design with escalating dose cohorts was to be used with this Phase I study starting at 1 mg/kg and escalating to 3 mg/kg. Subjects will be assigned to a dose level in the order of study entry. '*The first cohort will receive nivolumab at the 1 mg/kg dose level. Enrollment into the next cohort cannot begin until 2 weeks after the administration of the third dose (after 7 weeks) of nivolumab to the last patient in the previous cohort. Up to 6 subjects will be treated at each dose level with expansion to 9 subjects if two dose-limiting toxicities are observed in the first 6 subjects. If dose limiting toxicity occurs at the first dose level, the study of lower doses of nivolumab may be investigated*.'

7.2.4.2. Expansion cohorts

Four expansion cohorts were to be enrolled, with the haematologic malignancies selected based on the expression of PD-L1 by the tumour or expression of PD-1 on infiltrating T cells in the tumour. The selected malignancies were HL/PMBL, T cell lymphoma, B cell lymphoma and multiple myeloma. If none of the first 5 subjects have a DLT by the end of seven weeks of treatment in the dose escalation phase of the study, enrolment to the primary expansion cohorts can begin immediately following the enrolment of the sixth subject. Subjects in the expansion phase will be treated at the previously determined MTD or if no MTD is identified a maximum dose of 3 mg/kg.

7.2.5. Protocol amendments

Significant protocol amendment changes included:

- Amendment 02 (December 2012): eliminated the highest (10 mg/kg) of three dose levels scheduled to be examined

- Amendment 04 (June 2013): increased the size of the expansion cohorts from 16 to 23
- Amendment 07 (August 2014): added an additional set of cohorts (approximately 80 additional subjects) for dose expansion with combination of lirilumab and nivolumab
- Amendment 08 (November 2014): revised the protocol to meet FDA guidance
- Amendment 10 (April 2015): allowed retrospective collection of radiologic images for blinded independent central review.

Comment: The evaluator was unable to locate the reason(s) for elimination of the highest (10 mg/kg) of three dose levels (Amendment 02). See Question 17: Dose escalation phase of Study CA209039 in Section 11, below.

7.2.6. Inclusion and exclusion criteria

While the study enrolled and treated patients with relapsed refractory haematologic malignancies (multiple myeloma, non-Hodgkin lymphoma, Hodgkin lymphoma and T cell lymphoma), only the subjects with relapsed or refractory cHL and treated with nivolumab monotherapy are included in this interim CSR. Inclusion criteria for HL patients were: histologically confirmed evidence of relapsed or refractory Hodgkin's lymphoma with at least one lesion measuring more than 1.5 cm, ECOG performance-status score of 0 or 1, previous treatment with at least one chemotherapy regimen, and no autologous stem-cell transplantation within the previous 100 days.

Patients with moderate-severe renal or hepatic dysfunction, CNS lymphoma, concomitant secondary malignancy, active auto-immune disease, significant cardiovascular disease, prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti CTLA-4 antibody, prior organ allograft or allogeneic bone marrow transplantation, symptomatic interstitial pneumonitis were excluded.

WOCBP and sexually active fertile men with partners who were WOCB age were required to use effective contraception methods for the entire study period and for at least 23 weeks (WOCB) or 31 weeks (men) after the last dose of study drug.

7.2.7. Study treatments

Nivolumab 3 mg/kg therapy was given at Week 1. This first dose was followed by a three week period for pharmacokinetic and pharmacodynamic assessment of nivolumab. A response assessment following administration of the first dose will be obtained. Therapy was subsequently given every two week thereafter. Treatment was continued for up to 2 years or until confirmed complete remission (CR), confirmed progressive disease (PD), or unacceptable toxicity. Dose delays but not dose reductions were permitted. Disease status was monitored at all study visits by physical measurements and ECOG PS.

All the patients underwent computed tomography (CT) and 18F-fluorodeoxyglucose–positron-emission tomography (FDG-PET) at screening. Tumour response assessments using spiral CT scanning were performed at Weeks 4, 8, 16, 24 and then every 16 weeks thereafter. During study drug treatment, the scheduled response assessments were completed before the next dose of therapy. Following confirmation of CR by CT, patients ceased study drug for a minimum of 4 weeks, and then had PET scanning to verify CR status.

Subjects with cHL were evaluated by investigators per protocol defined International Workshop to Standardized Response Criteria for Lymphomas. Following protocol Amendment 10 in 2015, which allowed radiological images to be collected for independent central review, subjects with cHL were retrospectively evaluated by an IRRC per 2007 International Working Group (IWG) criteria for malignant lymphoma. The same efficacy endpoints were analysed for investigator assessed and IRRC assessed.

Comment: A description of the 'protocol defined International Workshop to Standardized Response Criteria for Lymphomas' is provided in an appendix of the study protocol

(interim CSR) [not reproduced here] together with the 2007 IWG criteria reproduced (see Table 1, above).[26] The International Working Group criteria for lymphoma were originally developed to assess response to cytotoxic chemotherapeutic agents and were first described 1999. The criteria were revised in 2007 such that application of the criteria required both CT and PET scanning.

According to the sponsor's document 'Identification of errors of fact and/or material omission in the for Opdivo (Nivolumab) (First round) Clinical Evaluation Report' the 'protocol defined Lymphoma Response Criteria' were based on the 2007 IWG Response Criteria and not the 1999 IWG Response Criteria and that this is supported by only the reference for the 2007 IWG criteria being included in the protocol reference list. The sponsor notes, however, that these protocol defined response criteria include included two components from 1999 IWG criteria that are not part of the 2007 criteria:

- Responses must last for at least 4 weeks off treatment.
- Previously involved nodes that were 1.1 to 1.5 cm in greatest diameter must have decreased to less than or equal to 1 cm or by more than 75 percent in the sum of the products of the greatest diameters.

From this clarification provided by the sponsor it appears that the 'protocol defined lymphoma response criteria' contain elements of both the 1999 IWG Criteria and the 2007 IWG Criteria. Given this, the term 'protocol defined lymphoma response criteria' should be used where the evaluator had referred to 1999 IWG Response Criteria. It is important to note that the sponsor's clarification states 'For IRRC assessment, 2007 IWG criteria were used in Study CA209039', that is, different response criteria were used by the investigators and the IRRC.

Subjects were followed for 100 days upon discontinuation for safety data collection. Subjects with ongoing disease control (ongoing CR, partial remission (PR) or stable disease (SD)) entered the first Follow-up period, during time patients no longer receive study drug but assessments were continued for 1 year.

Treatment could be continued despite initial radiological progression using the 'protocol defined lymphoma response criteria' with the rationale that: '*Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ('mixed response'). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until progression is both confirmed and found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans or other evaluations*'

During the follow-up period, subjects could reinitiate study therapy for up to 1 additional year upon confirmed disease progression after discussion and agreement with the sponsor's medical monitor. Tumour assessment data collected after the start of re-initiation therapy did not contribute to the efficacy endpoints. Subjects who completed 1 year of follow-up without evidence of disease progression were not considered eligible for re-initiation of study therapy. All subjects were to be followed for survival for 5 years after the initiation of study therapy, or until subject death, subject consent was withdrawn, subject was lost to follow up or the study was completed.

Concomitant treatments with topical, ocular, intranasal, intra-articular, and inhalational corticosteroids were permitted. Immunosuppressive doses (for example, prednisone

[26] Cheson B, et al. Revised Response Criteria for Malignant Lymphoma. 2007. J Clin Oncol;25(5):579-86.

> 10 mg/day or equivalent) and/or physiologic replacement doses of systemic corticosteroids (for example, prednisone 10 mg/day) were permitted in the context of treating adverse events.

7.2.8. Efficacy variables and outcomes

Efficacy endpoints were exploratory and included ORR, duration of response (DOR), CR and PR rates, time to CR and PR, and duration of CR and PR. All endpoints were assessed by investigators and by IRRC. Assessments by the investigators were in accordance with protocol defined Lymphoma Response Criteria, based on both the 1999 and 2007 IWG criteria. Assessment by IRRC was retrospective and in accordance with the 2007 International Working Group (IWG) criteria for malignant lymphoma. According to the interim CSR, the investigator assessed end-points were the primary efficacy measures.

The IRRC provided an independent assessment of tumour response and progression for all response evaluable subjects. Images and select clinical data were centrally reviewed and evaluated. Two trained radiologist reviewers independently performed the timepoint-by-timepoint imaging response evaluation for each subject. All assessments were reviewed by an adjudicator who selected the radiology review assessments he/she most agreed with. An oncology review was performed after the radiologic assessment. The oncology reviewer was to assess both the radiology results and available clinical data so as to provide a final overall assessment for each timepoint/visit and end-point determination.

Comment: The evaluator was unable to locate any description of training of the investigators in the assessment of radiological images using the protocol defined lymphoma response criteria, nor any description of any quality control measures. In the absence of both specific training and quality control measures, high inter-rater variability is to be expected. However, as tumour response by IRRC is also provided, this is less of an issue.

Specific training in assessment according to the IWG 2007 criteria was provided to the IRRC radiologists according to the Independent Review Charter.

From the Independent Review Charter: *'IRRC Reviewer training: For radiology reviewers, a minimum of 5 cases (training and/or testing) will be used to ensure effective training. One case will consist of at least 2 imaging timepoints for a given subject. An imaging timepoint will be composed of representative imaging that would typically be received for this trial based on the requirements described in 'Imaging and Tumour Assessment Schedule'.*

For oncology reviewer, a minimum of 5 cases (training and/or testing will be used to ensure effective training. Oncology training cases will be prepared by Parexel to be representative of the study population. Each oncology case will be a representative lymphoma case using radiology review results and clinical data, consisting of at least 2 visits for a given subject.'

Quality control measures were also undertaken to minimise intra-reader variability and inter-rater variability. Intra-reader variability was checked by random presentation of 10% of cases for re-review and comparison of results. Inter-rater variability was reduced by the double read ± adjudicator process and by proactive confirmation of appropriate use of the 2007 IWG criteria.

The IRRC quality control measures from the Independent Review Charter:

'Additionally, post-review data checks will be performed and outlier reports generated which are reviewed by the appropriate PAREXEL project team member to identify errors.

If a lack of adherence to the Charter-defined rules and criteria and/or completion of the eICRF/eOCRF are identified, PAREXEL medical personnel will:

- *Evaluate the discrepancy for the reviewer*
- *Determine its impact on the assessment results and/or study endpoints*
- *Formulate a recommended corrective action*

Corrective actions will include the communication of the review findings to the independent reviewer. Depending on the severity and complexity of the findings the form of communication may include:

- *Refresher e-mail to the independent reviewer*
- *Reminder phone call to the independent reviewer*
- *Online demonstration of the findings*
- *Face-to-face meeting with demonstration of the findings*

Any discrepant findings will be addressed as necessary by Post-Review Data change(s) or re-review(s).'

7.2.8.1. Endpoint definitions

Best Overall Response (BOR) is defined as the best response designation over the study as a whole, recorded between the date of first dose and the last efficacy assessment prior to subsequent therapy.

Objective Response Rate (ORR) is defined as the number of subjects whose BOR is either partial response (PR) or complete response (CR) divided by the number of treated subjects (or response-evaluable subjects).

Duration of Objective Response (DOR) is defined as the time when the measurement criteria are first met for objective response until the date of documented disease progression or death. For subjects who neither progress nor die, the duration of response will be censored at the date of their last disease assessment.

Time to Response (TTR) for a subject with a BOR of CR or PR is defined as the time from the first dosing date to the date of the first documented objective response (CR or PR).

Progression Free Survival Rate (PFSR) is defined as the proportion of subjects remaining progression free or surviving to time (t), where t = 8, 16 and 24 weeks for patients receiving monotherapy nivolumab.

Progression free survival (PFS), computed for all treated subjects, is defined as the time between date of first dose of study therapy and date of progression or death, whichever occurs first.

Following confirmation of investigator-assessed CR (as shown by persistence of response for a 4 week period), patients stopped study drug and were required to confirm this response with a PET after a minimum of 4 weeks to verify CR status.

Other outcome measures included:

Safety: The assessment of safety was based on the incidence of adverse events (AEs) including clinical laboratory test abnormalities, serious adverse events (SAEs), adverse events leading to discontinuation, select AEs, and deaths. Adverse events will be evaluated according to the NCI CTCAE Version 4.0. Subjects should be followed until all treatment-related adverse events have recovered to baseline or are deemed irreversible by the investigator.

Pharmacodynamics (biomarkers): A secondary objective was to assess the potential association between PD-L1 expression on tumour cells and clinical efficacy measures. Exploratory biomarkers were measured in tumour tissues and in peripheral blood: PD-L1 by DAKO/immunohistochemistry (IHC) assay, and PDL1, PD-L2, 9p24, pSTAT3, and EBV performed at the Dana Farber Cancer Institute (DFCI).

Immunogenicity: Immunogenicity of nivolumab was a secondary objective. Blood samples for immunogenicity analysis were collected. Samples testing positive in the nivolumab immunogenicity ADA assay were analysed for neutralising activity.

7.2.9. Randomisation and blinding methods

Not applicable.

7.2.10. Analysis populations

Populations for analysis in the 23 patients with cHL treated with nivolumab monotherapy 3 mg/kg were:

- All Treated cHL Subjects: All cHL subjects who received at least one dose of nivolumab 3 mg/kg monotherapy. This is the primary population for safety.
- cHL ASCT-Bren Failures Subjects: A subset of cHL subjects of whom with relapsed or refractory cHL after failure of ASCT and subsequent brentuximab vedotin. This is the primary population for efficacy.
- cHL Other Subjects: A subset of cHL excluding the cHL ASCT-Brenfailure subjects.
- Immunogenicity Population: Refer to immunogenicity SAP for nivolumab
- PD-L1 Evaluable Subjects: All treated cHL subjects with a quantifiable PD-L1 expression at Baseline.
- cHL subjects treated beyond progression: All treated cHL subjects who received at least one dose of nivolumab after the date of initial progression per protocol defined criteria based on investigator assessment.

7.2.11. Sample size

For the dose expansion cohorts, approximately 23 subjects are expected to be enrolled in each of four tumour types and treated at the previously determined MTD or if no MTD is identified a maximum dose of 3 mg/kg.

The following rationale for the sample size of 23 was provided: '*In an expansion cohort, if 4 (17.4%) or 5 (21.7%) responses are observed with 23 subjects in each cohort, then the lower limit of the 90% one-sided confidence intervals for the objective response rate would be 7.8% and 11.0% respectively. These calculations are based on the Clopper-Pearson method for exact confidence intervals*'.

1.1.1.1. Statistical methods

The statistical analysis plan (SAP) for the whole study (dose escalation and dose expansion phases) was not provided. According to the SAP provided: '*this document will describe statistical analyses that will be conducted for an interim Clinical Study Report (iCSR) based on classical Hodgkin Lymphoma (cHL) patients (N = 23) treated with nivolumab monotherapy (3 mg/kg for the first dose and then 3 mg/kg every 2 weeks), in support of a regulatory filing for the treatment with nivolumab monotherapy of patients with relapsed or refractory cHL after failure of autologous stem cell transplant (ASCT) and subsequent brentuximab vedotin'* and '*At the time of analysis, the duration of follow-up from last patient first treatment (LPFT) is approximately 84 weeks in this subset of subjects. Final analysis will be performed after all subjects have completed the study (after the follow-up periods) or have discontinued prematurely*'.

Continuous variables were summarized using descriptive statistics, that is, medians, minimums, maximums, and means with standard deviations/standard errors of the mean. Categorical variables were summarized by frequencies and percentages. Percentages were rounded and may not always add up to 100.

All efficacy and safety analyses were performed on by cHL ASCT-Bren Failed Subjects, cHL Other Subjects, and All Treated cHL Subjects.

Time to event distribution (for example; progression free survival, overall survival, and duration of response) were estimated using the K-M method. When appropriate, the median along with 95% CI was provided using Brookmeyer and Crowley methodology. Rates at fixed

time points (for example, PFSR at 6 months or OS at 12 months) were derived from the K-M estimate.

Sensitivity analyses were performed for DOR and PFS based on both investigator assessment and IRRC assessment using an alternative censoring scheme.

Comment: Results in the CSR were presented for two distinct subgroups, 15 subjects with a treatment history identical to Cohort B from Study CA209205, who had prior brentuximab vedotin treatment after failure of ASCT (the 'cHL ASCT-Bren Failed' group) and the 'other group'. The related article divided the 'other group' into two, one group of 3 patients who had received brentuximab vedotin before or without ASCT and one group of 5 patients who had not received brentuximab vedotin.

1.1.1.2. Participant flow

There were 23 cHL patients enrolled and treated with nivolumab as monotherapy (3 mg/kg). Of these 15 patients had relapsed or refractory cHL following brentuximab vedotin as rescue therapy for failed ASCT; another 3 patients had received brentuximab vedotin but not in this sequence.

At the time of this report:

- 3/23 patients remained on treatment with investigator assessed response of PR and had not yet reached 2 years of treatment.
- 20/23 patients were off treatment. Reasons for discontinuing treatment were:
  - 6 due to disease progression
  - 2 due to study drug toxicity (pancreatitis, myelodysplastic syndrome [MDS])
  - 2 due to subject request (one patient chose to have allogeneic SCT, one patient request due to joint and muscle pain)
  - 4 due to other reasons (patient to receive 'bone marrow transplant' n = 1, ASCT n = 1, allogeneic SCT n = 2), one of these patients had achieved CR
  - 4 had achieved CR
  - 2 had completed the maximum of 2 years of treatment.

Of the 20 patients who were off study treatment 13 were in follow-up, 5 had died, 2 were lost to follow up.

For the 15 ASCT-Bren Failed group:

- 2 patients were continuing with study drug treatment
- 13 patients had discontinued study drug treatment for the following reasons:
  - 5 patients due to disease progression
  - 2 patients due to study drug toxicity (pancreatitis and MDS)
  - 3 at their own request or for 'other reason'
  - 2 patients had achieved confirmed CR per investigator
- One patient had completed 2 years of therapy.

7.2.12. Major protocol violations/deviations

According to the interim CSR, there were two significant protocol deviations for cHL subjects reported. Protocol deviations for other groups were not described.

Table 34. Protocol deviations affecting cHL patients

Category classification	Deviation description
Failure to obtain written informed consent prior to each subject's participation in the study.	Subject was treated beyond confirmed progression however did not re-sign a copy of the ICF at that time.
Other	Subject did not receive pregnancy test from Day 1 to Week 32. Pregnancy test was negative at screening and at Week 34.

7.2.13. Baseline data

The majority of all cHL subjects were White (20/23, 87%). All 23 patients had been extensively pre-treated with a median of 5 prior regimens (range 2 to 15) and 87% having received three or more previous treatment regimens. 18 patients had received brentuximab vedotin previously, and 18 had undergone autologous stem-cell transplantation. Of the patients who had received brentuximab vedotin, 15/18 had received brentuximab vedotin treatment as a salvage therapy after failure of ASCT, one had received brentuximab vedotin prior to an ASCT and two had received brentuximab vedotin but had not had an ASCT before or after.

The most common site of lesions other than lymph nodes was lung (34.8%) and other sites included liver (13.0%) and kidney (4.3%). No subjects in the study had CNS disease.

For the ASCT-Bren Failed group, the median age was 40 years (range 24 to 54), 10/15 patients were male, 12/15 were white with 2 black and one 'other'.

Comment: Not all baseline data was provided separately for the ASCT-Bren Failed group in the interim CSR.

Baseline data is reproduced below in Table 35.[27]

[27] Ansell S, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015;372:311-9.

Table 35. Baseline data

Characteristic	Value
Age — yr	
Median	35
Range	20–54
Male sex — no. (%)	12 (52)
Race — no. (%)*	
White	20 (87)
Black	2 (9)
Other	1 (4)
ECOG performance-status score — no. (%)†	
0	6 (26)
1	17 (74)
Histologic findings — no. (%)	
Nodular sclerosis	22 (96)
Mixed cellularity	1 (4)
No. of previous systemic therapies — no. (%)	
2 or 3	8 (35)
4 or 5	7 (30)
≥6	8 (35)
Previous treatment — no. (%)	
Brentuximab vedotin	18 (78)
Autologous stem-cell transplantation	18 (78)
Radiotherapy	19 (83)
Extranodal involvement — no. (%)‡	4 (17)

* Race was either self-reported or reported by investigators.
† Eastern Cooperative Oncology Group (ECOG) scores indicate the performance status of patients with respect to activities of daily living on a scale from 0 to 5, with higher numbers indicating greater disability. A score of 0 indicates that the patient is fully active and able to carry out all predisease activities without restriction, and a score of 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light nature.
‡ Sites of extranodal disease were bone, lung, pelvis, peritoneum, and pleura.

7.2.13.1. Study drug exposure

The majority of subjects (18/23, 78.3%) received ≥ 90% of the planned dose intensity and the remaining subjects received 70% to < 90%. The median number of cycles was 18 (range 6 to 48).

For the ASCT-Bren Failed group (n = 15), the majority of subjects (11/15, 73.3%) received ≥ 90% of the planned dose intensity and the rest received 70 to 90%. The median number of doses received was 24 (range: 6 to 48 doses). Two subjects from the ASCT-Bren Failed group stopped treatment due to investigator-assessed CR after 10 and 40 doses, respectively.

Eleven subjects (11/23, 47.8%) had at least 1 dose delay during the study: 9 (60%) of these were ASCT-Bren Failed subjects. Fifty percent of the dose delays reported was attributed to 'other' personal or administrative reasons (for example visits rescheduled). The other 50% of dose delays were because of non-haematologic toxicity with reasons that included rash, cough/viral illness, vomiting, pain, thumb infection, sinusitis, flu, lung infection, bronchospasm, pneumonia, muscle pain and Grade 2 lipase elevation. No subject reported a dose delay for haematologic toxicity. All subjects were able to continue on study drug after these dose delays

Three subjects, all from the cHL ASCT-Bren Failed group reported infusion interruptions due to Grade 1 or 2 hypersensitivity reactions (n = 2) and infusion administration difficulties (infusion line disconnected) (n = 1). One subject reported recurrent infusion interruption for hypersensitivity reaction.

7.2.13.2. Subsequent cancer therapy

A total of 12 cHL subjects reported subsequent cancer therapy: 8 were from the cHL ASCT-Bren Failed group and 4 from the cHL Other group.

SCT: 5 received allo-SCT and 1 received ASCT; following a BOR of CR per investigator (n = 1), PR (n = 5):

- Four patients received allo-SCT only
- One patient had combination chemotherapy with doxorubicin, gemcitabine and vinorelbine) with allo-SCT several months later
- One patient had ASCT followed several months later by radiotherapy and several months later by brentuximab vedotin.

Of the 6 patients, at the time of the interim analysis, 3 had died and 2 had developed GVHD.

Other therapies: 6 patients had received other subsequent cancer therapy

- 5 who discontinued study drug treatment due to PD received subsequent therapies of:
  - One patient received mantle radiation
  - One patient received a combination of brentuximab vedotin and ipilimumab
  - One patient received bendamustine
  - One patient received combination chemotherapy with adriamycin, etoposide, vincristine; rituximab; and prednisone
  - One patient received brentuximab vedotin followed by radiotherapy (TBI) several months later.
- One patient with SD at time of treatment discontinuation due to drug toxicity (pancreatitis) had two subsequent regimens, an investigational immunomodulating therapy then combination therapy with panobinostat + everolimus.

7.2.14. Results for the efficacy measures

The median extent of follow-up for all 23 cHL subjects was 23.3 months (Min, Max: 7.3, 27.8). The median extent of follow-up for the 15 ASCT-Bren Failed patients was 22 months (range 11.2 to 27.6).

A summary of the efficacy results is shown in Table 36, below.

Table 36. Study CA209039 Summary of clinical efficacy results

	Number of Subjects (%)					
Efficacy Parameters	**IRRC Total Subjects (n=23)**	**Investigator Total Subjects (n=23)**	**IRRC ASCT-Bren Failed (n=15)**	**Investigator ASCT-Bren Failed (n=15)**	**IRRC cHL Other (n=8)**	**Investigator cHL Other (n=8)**
ORR	14 (61)	20 (87)	9 (60)	13 (87)	5 (63)	7 (88)
CR	3 (13)	5 (22)	0	2 (13)	3 (38)	3 (38)
PR	11 (48)	15 (65)	9 (60)	11 (73)	2 (25)	4 (50)
SD	7 (30)	3 (13)	5 (33)	2 (13)	2 (25)	1 (13)
Objective Response Achieved						
Within 9 weeks	13 (57)	11 (48)	8 (53)	8 (53)	5 (63)	3 (38)
Within 4 months	13 (57)	16 (70)	8 (53)	11(73)	5 (63)	5 (63)
Within 6 months	14 (61)	18 (78)	9 (60)	13 (87)	5 (63)	5 (63)
Within 12 months	14 (61)	20 (87)	9 (60)	13 (87)	5 (63)	7 (88)
No. of Subj. Evaluated for TTR and DOR (F)	14	18	9	12	5	6
Time to Response (months) Median (Min, Max)	1.2 (0.7, 4.1)	1.7 (0.7, 9.2)	0.8 (0.7, 4.1)	1.7 (0.7, 5.7)	1.6 (0.7, 1.6)	2.6 (1.6, 9.2)
Time to CR (months) Median (Min, Max) (C)	12.5 (5.4, 21.8)	5.3 (1.6, 19.9)	NC	10.8 (1.6, 19.9)	12.4 (5.4, 21.8)	5.3 (4.4, 9.2)
Time to PR (months) Median (Min, Max) (D)	0.8 (0.7, 4.1)	1.7 (0.7, 8.9)	0.82 (0.7, 4.1)	1.7 (0.7, 5.7)	1.17 (0.7, 1.6)	3.5 (1.6, 8.9)
DOR Median (95% CI) (B)	N.A. (7.43, N.A.)	N.A. (15.5, N.A.)	12.0 (1.8, N.A.)	N.A. (8.3, N.A.)	N.A. (1.9, N.A.)	N.A. (17.0, N.A.)
No. of Subj. with DOR of at Least						
12 months	6 (43)	9 (50)	3 (33)	7 (58)	3 (60)	2 (33)
18 months	4 (29)	4 (22)	2 (22)	3 (25)	2 (40)	1 (17)
Ongoing Response (E) (F)	5 (36)	7 (39)	3 (33)	5 (42)	2 (40)	2 (33)

B) Median computed using K-M method; C) Subjects with BOR of CR; D) Subjects with BOR of PR; E) Subjects with ongoing response include responders who had neither progressed nor initiated subsequent therapy at time of analysis, and excludes responders censored prior to 26 weeks of the clinical cut-off date; F) 2 subjects who had investigator assessed disease progression per protocol criteria before achieving response are excluded from calculation.

7.2.14.1. Objective response rate

Assessment per investigator was by the investigator interpreting the regular CT scans according to the 'protocol defined lymphoma response criteria' together with available clinical information. A protocol amendment in April 2015 allowed central review of scans. The last patient visit occurred in June 2015. Assessment per IRRC following this amendment was retrospective review of CT scans and PET scans by two independent radiologists using the 2007 IWG criteria followed by oncologist review of the radiological assessment and clinical information.

For all 23 patients, at the time of DBL, the ORR was 61% per IRRC. Of the 14 responders per IRRC, 3 had CR and 11 had PR. A further 7 had SD per IRRC.

For the 15 ASCT-Bren Failed patients, the ORR was 60% per IRRC. Of the 11 responders per IRRC, 0 had CR and 9 had PR. A further 5 patients had SD per IRRC.

Comment: The results for ORR show some discordance between the investigator assessments and IRRC assessments that may reflect inter-rater variability and bias. The discordance was attributed by the sponsor to '*alternative interpretation of the PET scan between the investigator and IRRC, different choice and assessment of new lesions and target lesions'*. The evaluator notes, in an appendix of the CSR, that for 12/23 patients there were discordant assessments by the two IRRC radiologists, with differences ranging from PD versus CR, SD versus PD, SD versus CR, PR versus

CR, PR versus SD. These differences occurred despite specific training in the use of the 2007 IWG criteria and were resolved by the third radiologist. For 8/12 of these patients, there was disagreement between the investigator assessment and the IRRC assessment of BOR: for 5/8, the investigator assessment was CR/PR compared to the IRRC of SD/PD; for 1/8, investigator assessment was SD compared to the IRRC of PR; for two patients the disagreement was between PR and CR. Applying the IWG criteria to radiological images appears to be a complex process in some patients. These discrepancies raise considerable concerns regarding the reliability of the investigator assessments, which were determined by one person with no apparent specific training reading the scans. There is also the potential for bias on the part of the investigators in this open label single arm study.

It is also possible that discrepancies occurred due to differences in the response criteria provided the investigators compared to the 2007 IWG Criteria used by the IRRC.

7.2.14.2. Time to respond

In 11/20 responders per investigator and 13/14 responders per IRRC, the BOR response occurred within 9 weeks of commencing treatment. However, in some patients, BOR was not achieved for 6 months or longer. In one patient, CR was achieved after 21 months of treatment.

Of the 15 ASCT-Brenfailed patients, the BOR response occurred within 9 weeks of commencing treatment in 8/13 responders per investigator and 8/9 responders by IRRC (range 2 to 16 weeks).

7.2.14.3. Duration of Response

The median DOR was not reached for the group of 23 patients. There were 5/14(36%) per IRRC responders who had an on-going response at the time of DBL and 6/14 (43%) of responders per IRRC who had a DOR of at least 12 months. The range of duration of response was 1.8 to 23 months.

In the ASCT-Bren Failed group, the KM estimated median DOR per IRRC was 12.0 months (95% CI 1.8, N.A.). There were 3/9(33%) per IRRC responders who had an on-going response at the time of DBL and 3/9 (33%) of responders per IRRC who had a DOR of at least 12 months. The range of duration of response was 1.8 to 23 months.

Figure 19. Duration of response per IRRC

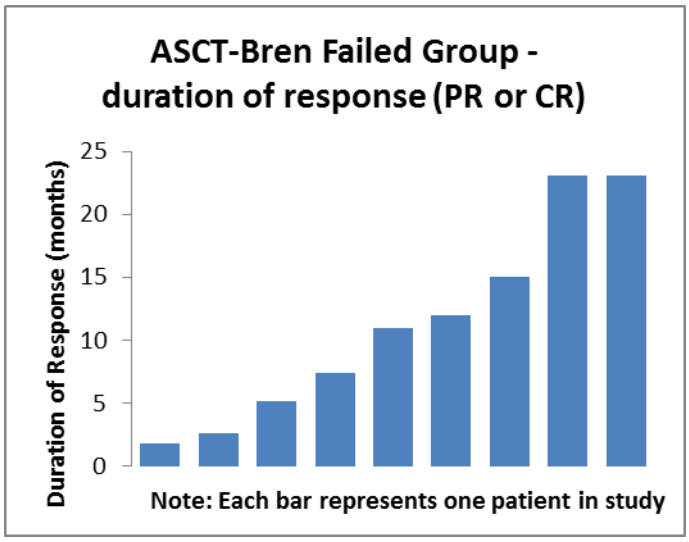


Table 37. Duration of response per IRRC for the ASCT-Brenfailed group

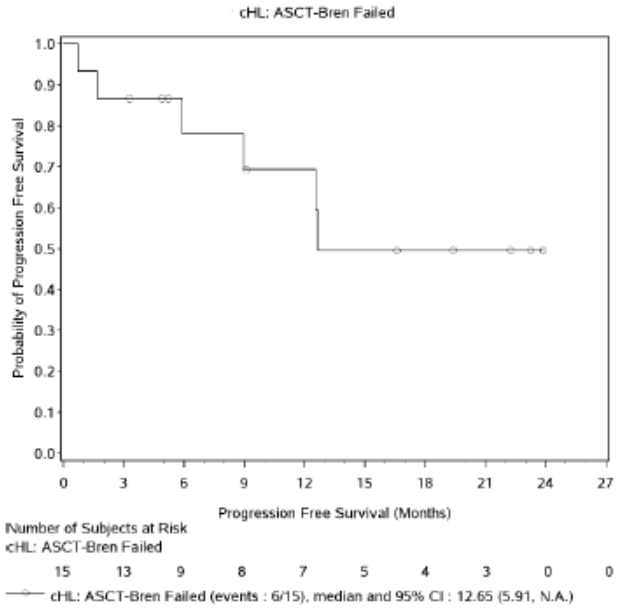
Patient number	Duration of Response (months)	At time of censoring for duration of response
1	1.8	PD
2	2.6	received subsequent anti-tumour therapy
3	5.1	received subsequent anti-tumour therapy
4	7.4	PD
5	11	PD
6	12	PD
7	15	in follow-up
8	23.1	on treatment
9	23.1	in follow-up

An event chart was provided for the responses per investigator but not per IRRC in the interim CSR [not reproduced here].

7.2.14.4. Progression free survival (PFS) per IRRC

There were 8 progression events (6 in the ASCT-Brenfailed group) per IRRC during the period of follow-up. Based on the IRRC assessment of PFS, the KM estimate of median PFS for ASCT-Brenfailed was 12.7 months (95% CI, 5.91, N.A) and not reached for all cHL subjects. The K-M curve for the ASCT-Brenfailed group is shown in Figure 20, below.

Figure 20. K-M plot of PFS per IRRC for the cHL ASCT-Brenfailed group



7.2.14.5. Overall Survival (exploratory endpoint)

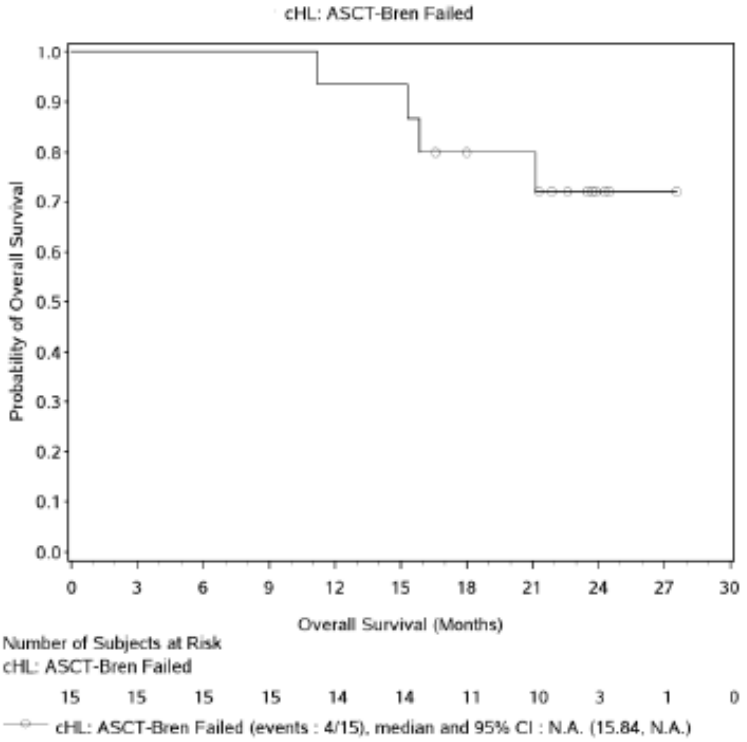
At the time of database lock for this interim report, with median follow-up of 23 months (range 7 to 28 months), 5 patients had died (21.7%), with 4 of these patients in the ASCT-Bren Failed group (4/15, 26.7%) as shown in Table 38, below.

Table 38. Overall survival

	cHL: ASCT-Bren Failed N = 15	cHL: Other N = 8	cHL: All N = 23
# EVENTS / # SUBJECTS (%)	4/15 (26.7)	1/8 (12.5)	5/23 (21.7)
MEDIAN OS (MONTHS) (95% CI)	N.A. (15.84, N.A.)	N.A. (7.33, N.A.)	N.A.
1 YEAR			
N AT RISK	14	7	21
OS RATE (95% CI)	93.3 (61.3, 99.0)	87.5 (38.7, 98.1)	91.3 (69.5, 97.8)
1.5 YEARS			
N AT RISK	11	7	18
OS RATE (95% CI)	80.0 (50.0, 93.1)	87.5 (38.7, 98.1)	82.6 (60.1, 93.1)
2 YEARS			
N AT RISK	3	4	7
OS RATE (95% CI)	NC	NC	NC

The estimated median OS was not reached for cHL all subjects and the 2 subgroups (ASCT-Brenfailed group and cHL Other group). A K-M plot for OS is shown in Figure 21, below.

Figure 21. K-M plot of OS for the ASCT-Brenfailed group



7.2.14.6. Treatment beyond disease progression

Patients could be continued on study drug treatment beyond protocol defined disease progression (as assessed by the investigator) at the discretion of the investigator. According to a table [not reproduced here] of the interim CSR, there were 7 progression events per investigator during the period of follow-up. Of these 7 patients, 4 were treated beyond disease progression. According to the definition of BOR per investigator, 3 of these subjects were subsequently classified as responders:

- ASCT-Bren Failed group:
  - One patient achieved PR followed by disease progression. Disease progression persisted despite continuation of treatment.
  - One patient had initial disease progression followed by PR with ongoing study drug treatment with disease progression then occurring after approximately 12 months of treatment.

- Other cHL group
  - One patient had an 'unconventional response' with increase in tumour burden initially and then PR with study drug continuation. The patient subsequently discontinued treatment and underwent alloSCT.
  - One patient had initial disease progression. With continued study drug treatment, there was a reduction in tumour burden but not sufficient to reach PR. Disease progression subsequently occurred.

Comment: It is not clear as to how the decision was made to treat 4/7 patients beyond progression and to not treat 3/7 patients Question 23: Treatment beyond progression in Study CA209039.

7.2.14.7. Results in ASCT-naive subjects

Of the 23 subjects enrolled in the cHL expansion of Study CA209039 and treated with nivolumab 3 mg/kg Q2W, 5 were ASCT-naïve (3 were also 'brentuximab-naïve'). Of these 5 patients, 4 had an objective response to nivolumab, although only one was continuing in treatment at the time of analysis:

- One had ceased treatment following confirmation of CR as per protocol, with DOR of 24 months
- 2 had ceased treatment to undergo ASCT
- One ceased treatment due to disease progression and proceeded to treatment with brentuximab vedotin and radiotherapy.
- Results are summarised in Table 39, below.

Table 39. Summary of results for ASCT-naïve patients

BOR		TTR (months)		DOR (months)			
IRRC	INV	IRRC	INV	IRRC	INV	Prior Bren	Disposition
CR	PR	1.6	1.6	24.0	23.8	Yes	Discontinued due to reaching maximum clinical benefit per protocol.
SD	PR	NA	3.4	NA	2.3	No	Elected to stop Nivo after response and underwent subsequent SCT.
PR	SD	1.6	NA	1.9	NA	No	Discontinued for disease progression (new lesion). Subsequent therapy: Bren and radiotherapy.
CR	CR	1.6	1.6	4.4	3.8	No	Elected to stop Nivo after response and underwent subsequent SCT.
CR	PR	0.7	8.9	21.7	11.9	Yes	Still continuing in treatment period.

Note: Each row represents a single ASCT-naïve patient.

7.3. Integrated analysis of efficacy

An integrated analysis of efficacy is provided in the Clinical Overview and the Summary of Clinical Efficacy. According to the Summary of Clinical Efficacy (SCE), it '*presents efficacy data from a prospectively planned integrated analysis that includes a total of 95 cHL subjects from these 2 studies (80 subjects from Study CA209205 and 15 subjects from Study CA209039) along with the data from individual studies'*. The integrated analysis was possible as all subjects '*had prior brentuximab treatment after failure of ASCT and were treated with nivolumab 3 mg/kg*

Q2W' and the efficacy end-points in each study were assessed by an Independent Radiologic Review Committee (IRRC) using the 2007 revised International Working Group criteria for Malignant Lymphoma (2007 IWG criteria).

The integrated analysis was conducted after subjects in Study CA209205 Cohort B met the minimum follow-up of 6 months from last patient first treatment (LPFT) for the analysis of primary endpoint of ORR. At the time of database lock for Study CA209205 Cohort B, the cHL expansion cohort in Study CA209039 for nivolumab monotherapy, including the 15 subjects in the Study CA209039 ASCT-Bren Failed group, had a minimum follow-up of approximately 18 months.

Comment: The evaluator was unable to locate a description of the prospective plan for an integrated analysis in the SAP or interim CSR of either study. It may be more appropriate to consider this as a post hoc analysis rather than 'prospective' analysis. In support of this, the evaluator notes:

1. Evaluation of end-points by an independent IRRC was a very late protocol amendment in Study CA209039, occurring in April 2015 although recruitment commenced in December 2012. Database lock for Study CA209039 was August 2015.
2. The minimum duration of follow-up of 6 months for Cohort B in Study CA209205 was a protocol amendment in May-June 2015 from the original August 2014 protocol, which specified that analysis was to occur after minimum follow-up of 12 months for Cohort B. Database lock for Study CA209205 was August 2015.
3. Differing definitions of BOR were used in each study:
    a. Study CA209039 defined investigator assessed BOR as the best response designation recorded between the date of first dose and the last efficacy assessment prior to subsequent anticancer therapy.
    b. Study CA209205 defined BOR as the best response designation recorded between the date of first dose and the date of initial documented progression per the 2007 IWG criteria or the date of subsequent anticancer therapy, whichever occurred first.
4. Differing methods of tumour response assessment and different scheduling of FDG-PET scans:
    a. Tumour response in Study CA209205 was by both investigators and IRRC applying the 2007 IWG criteria, with FDG-PET scans performed at Baseline, at Weeks 17 and 25, and to confirm to confirm any radiographic CR responses.
    b. Tumour response assessments in Study CA209039, until the April 2015 amendment, were only made by investigators using protocol defined Lymphoma Response Criteria. According to the study protocol (Appendix 1.1 of the interim CSR, page 1373), these criteria were based on the *'International Workshop to Standardize Response Criteria for non-Hodgkin's Lymphomas',* that is, the 1999 IWG criteria. Protocol scheduled FDG-PET scans were at screening and to confirm any radiographic CR responses. The IRRC used the 2007 IWG criteria but without any regularly scheduled FDG-PET scans post-baseline.

    The criteria used by the investigators in Study CA209039 was clarified in the sponsor's document 'Identification of errors of fact and/or material omission in the for Opdivo (Nivolumab) Clinical Evaluation Report'. According to this, the 'protocol defined Lymphoma Response Criteria' used by the investigators in Study CA209039 were based on the 2007 IWG Response Criteria but did include two components from 1999 IWG criteria that are not part of the 2007 criteria:

        i. Responses must last for at least 4 weeks off treatment.

ii. Previously involved nodes that were 1.1 to 1.5 cm in greatest diameter must have decreased to less than or equal to 1 cm or by more than 75 percent in the sum of the products of the greatest diameters.

It appears that the 'protocol defined lymphoma response criteria' contain elements of both the 1999 IWG Criteria and the 2007 IWG Criteria and that these criteria are not the same as the 2007 IWG criteria used by the IRRC in Study CA209039 and the investigators and IRRC in Study CA209205.

5. Inclusion criteria for Study CA209205 specified that an FDG-PET scan avid lesion must be present; this was not required in Study CA209039.
6. Criteria for ceasing treatment differed between the studies:
   a. Study CA209205: Treatment was continued until unacceptable toxicity or disease progression.
   b. Study CA209039: Treatment was continued until disease progression, PET-scan confirmed CR, unmanageable drug toxicity, patient choice or for a maximum of 2 years.

   Treatment could be continued after disease progression at the investigator's discretion in both studies.

   It is not clear to the evaluator that any additional information or understanding of possible efficacy can be gained through the combination of results from these two different studies. Given this, the results presented by the sponsor in the Integrated Summary of Clinical Efficacy are briefly summarised below.

The Integrated Analysis of Efficacy combined Cohort B from Study CA209205 (n = 80) and the ASCT-Brenfailed group from Study CA209039 (n = 15). At the time of the analysis, the median follow-up was 9.46 months in the Integrated Population: 8.92 months in Study CA209205 Cohort B and 21.88 months in the CA209039 ASCT-BrenFailed group.

7.3.1. Participant Disposition

Disposition of the patients at the time of analysis is shown in Table 40 below.

Table 40. Integrated analysis, patient disposition

	CA209205 Cohort B + CA209039 cHL: ASCT-Bren Failed N=95	CA209205 Cohort B N=80	CA209039 cHL: ASCT-Bren Failed N=15
SUBJECTS	95	80	15
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	53 (55.8)	51 (63.8)	2 (13.3)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	42 (44.2)	29 (36.3)	13 (86.7)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)			
DISEASE PROGRESSION	18 (18.9)	13 (16.3)	5 (33.3)
STUDY DRUG TOXICITY	6 (6.3)	4 (5.0)	2 (13.3)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	4 (4.2)	2 (2.5)	2 (13.3)
LOST TO FOLLOW-UP	1 (1.1)	1 (1.3)	0
MAXIMUM CLINICAL BENEFIT	3 (3.2)	0	3 (20.0)
OTHER	9 (9.5)	8 (10.0)	1 (6.7)
NOT REPORTED	1 (1.1)	1 (1.3)	0
SUBJECTS CONTINUING IN THE STUDY (%) (A) (B)	88 (92.6)	74 (92.5)	14 (93.3)
SUBJECTS NOT CONTINUING IN THE STUDY (%) (B)	6 (6.3)	5 (6.3)	1 (6.7)
NOT REPORTED (%)	1 (1.1)	1 (1.3)	0
REASON FOR NOT CONTINUING IN THE STUDY (%)			
DEATH	1 (1.1)	1 (1.3)	0
SUBJECT WITHDREW CONSENT	2 (2.1)	2 (2.5)	0
LOST TO FOLLOW-UP	2 (2.1)	2 (2.5)	0
OTHER	1 (1.1)	0	1 (6.7)

Percentages based on subjects entering period or continuing study
(A) Includes subjects still on treatment and subjects off treatment continuing in the Follow-up period
(B) Subject status at end of treatment

7.3.1.1. Prior cancer therapies

The median number of prior systemic regimens excluding preparative regimens for ASCT was 5 (range: 2 to 15) with 51.6% of the subjects receiving 5 or more previous regimens. Most subjects (85.3%) received ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) as first-line prior regimen, and ICE (ifosfamide, carboplatin, and etoposide) was the most frequently used second-line regimen (34.7%). All subjects had ASCT including 8 who had ASCT twice (6 from Study CA209205 Cohort B and 2 from Study CA209039 ASCT-BrenFailed group). The majority (75.8%) of the subjects had prior radiotherapy.

Of the individual agents administered:

- All 95 subjects had prior brentuximab vedotin.
- Most of the 95 subjects received doxorubicin (97.9%), bleomycin (95.8%), vinblastine (90.5%), and dacarbazine (89.5%).
- Other more frequently (> 50% of the pooled population) administered chemotherapies included etoposide (78.9%), ifosfamide (72.6%), and gemcitabine (67.4%).

7.3.2. Overall Summary of Clinical Efficacy

The ORR per IRRC was consistent across the two studies (66.3% and 60.0%). The breakdown of results is shown in Table 41 below.

Table 41. Integrated summary of clinical efficacy, summary of ORR and DOR per IRRC

	Integrated Population N=95		CA209205 Cohort B N=80		CA209039 ASCT-Bren Failed Group N=15	
	IRRC	INV	IRRC	INV	IRRC	INV
ORR[a], n (%)	62 (65.3)	71 (74.7)	53 (66.3)	58 (72.5%)	9 (60.0)	13 (86.7)
95% CI	(54.8, 74.7)	(64.8, 83.1)	(54.8, 76.4)	(61.4, 81.9)	(32.3, 83.7)	(59.5, 98.3)
CR Rate, n (%)	7 (7.4)	24 (25.3)	7 (8.8)	22 (27.5)	0	2 (13.3)
95% CI	(3.0, 14.6)	(16.9, 35.2)	(3.6, 17.2)	(18.1, 38.6)	(0, 21.8)	(1.7, 40.5)
PR Rate, n (%)	55 (57.9)	47 (49.5)	46 (57.5)	36 (45.0)	9 (60.0)	11 (73.3)
95% CI	(47.3, 68.0)	(39.1, 59.9)	(45.9, 68.5)	(33.8, 56.5)	(32.3, 83.7)	(44.9, 92.2)
SD Rate, n (%)	23 (24.2))	20 (21.1)	18 (22.5)	18 (22.5)	5 (33.3)	2 (13.3)
DOR[b] (months)						
Events/Responders	15/62	12/70	11/53	9/58	4/9	3/12
Median[c] (95% CI)	8.74 (6.83, NA)	15.51 (8.25, NA)	7.79 (6.64, NA)	9.10 (6.74, NA.)	11.96 (1.84, NA)	NA (8.25, NA)
Min, Max[d]	0.0+, 23.1+	0.0+, 23.1+	0.0+, 9.5+	0.0+, 9.5+	1.8, 23.1+	1.5, 23.1+
Duration of CR[e] (months)						
Events/Responders	1/7	1/24	1/7	1/22	Not applicable	0/2
Median[c] (95% CI)	4.63 (NA, NA)	NA (8.74, NA)	4.63 (NA, NA)	8.74 (NA, NA)	Not applicable	NA (NA, NA)
Min, Max[d]	0.7+, 4.6	0.0+, 15.0+	0.7+, 4.6	0.0+, 8.7	0	3.4+, 15.0+
Duration of PR[f] (months)						
Events/Responders	14/55	11/46	10/46	8/36	4/9	3/10
Median[c] (95% CI)	8.74 (6.83, NA)	15.51 (6.74, NA)	7.79 (6.64, NA)	7.79 (6.74, 7.79)	11.96 (1.84, NA)	NA (1.54, NA)
Min, Max[d]	0.0+, 23.1+	0.0+, 23.1+	0.0+, 9.5+	0.0+, 7.8	1.8, 23.1+	1.5, 23.1+

There were a number of patients with ongoing response per IRRC at the time of the analysis, although the proportion was much lower in Study CA209039 which had a longer follow-up:

- 33/53 (62%) in Study CA209205 after median follow-up of 9 months
- 3/9 (33%) in Study CA209039 after median follow-up of 22 months.

Median PFS per IRRC was similar across the two studies:

- 9.99 months (95% CI 8.41, NA) in Study CA209205
- 12.65 (95% CI 5.91, NA) in Study CA209039.

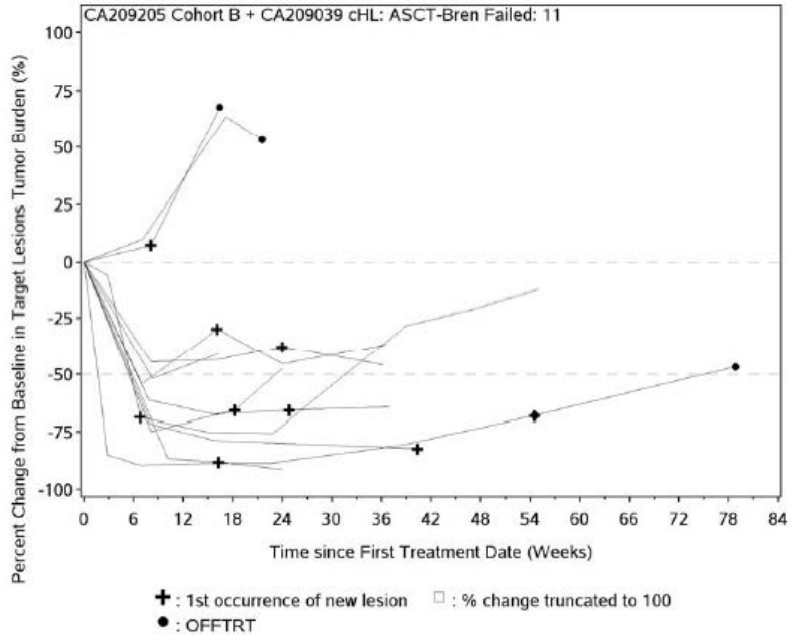
OS results were immature in both studies, with median OS not reached at 9 months in Study CA209205 and 22 months in Study CA209039.

7.3.2.1. Treatment beyond Progression

Treatment with nivolumab could be continued in the presence of 'non-conventional responses' despite progression according to the strict application by the investigator of the 1999 IWG criteria (Study CA209039) or the 2007 IWG criteria (Study CA209205).

In the Integrated Population, there were 11 subjects (9 from Study CA209205 and 2 from Study CA2090239) who had progressed as assessed by investigator but were considered eligible per protocol for ongoing nivolumab therapy. The number of nivolumab doses received beyond progression ranged from 1 to 21. Tumour reduction relative to baseline continued over time in most subjects (8/11) despite the appearance of new lesion in some cases.

Figure 22. Plot of tumour burden change per investigator, all evaluable subjects treated beyond progression



Response Evaluable: Subjects with i) a BOR of CR, PR, SD or PD, ii) target lesion(s) assessed at baseline, and iii) at least one on-study timepoint with all baseline target lesion(s) assessed. Horizontal reference line indicates the 50% reduction consistent with response criteria. Assessments are per Revised International Working Group Criteria for Malignant Lymphoma (2007) for CA209-205 and per International Workshop to Standardize Response Criteria for Lymphomas for CA209-039. Subjects treated beyond progression are defined as subjects whose last available dose date is after the date of initial progression per response criteria.

7.4. Evaluator's conclusions on clinical efficacy

For the indication of:

> *'Opdivo, as monotherapy is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin,*
>
> *or*
>
> *after at least two prior therapies in patients who are not candidates for ASCT.'*

As the indication is in two parts, the following discussion of efficacy is also in two parts.

7.4.1. Part 1: treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin

To demonstrate efficacy, the sponsor has provided interim analyses of two early phase studies:

- Study CA209205: analysis of one cohort of 80 patients from the open label single arm multiple cohort Phase II study
- Study CA209039: analysis of one sub-group of 15 patients from the escalation phase of an open label single arm multiple cohort Phase I study.

An integrated analysis of the efficacy results from these two studies was also provided.

The primary efficacy endpoint of each analysis was the surrogate endpoint of objective response rate and the population studied was patients with cHL who had developed progressive disease following ASCT followed by brentuximab vedotin used as rescue therapy overall survival and progression free survival were exploratory or secondary end-points in each study. No comparator was provided in either study.

7.4.1.1. Study CA209205

Study CA209205 was a non-comparative, single arm, multiple cohort, open label, Phase II study of nivolumab in patients with classical HL after failure of ASCT. The interim CSR provided with the submission presents the results of Cohort B from the study: 80 patients with relapsed/refractory cHL who had received brentuximab vedotin as salvage therapy after ASCT and who were treated with nivolumab monotherapy 3 mg/kg every 2 weeks. Treatment was continued until disease progression or toxicity, or other reasons for discontinuation. Patients were able to continue to receive nivolumab beyond disease progression at the discretion of the investigator. During treatment, patients had regularly scheduled CT scans and PET scans. PET scans were also required to confirm radiological CR.

The primary efficacy end-point was objective response rate per IRRC with this defined as the proportion of subjects achieving best overall response (BOR) of either a partial remission (PR) or complete remission (CR) according to the revised International Working Group criteria for Malignant Lymphoma (2007 IWG criteria). Following a late protocol amendment, the time of analysis for cohort B was reduced from 12 months to 6 months after the last enrolled subject's first dose of study therapy. Other efficacy end-points included duration of response per IRRC, PFS per IRRC and OS. Health-related quality of life was assessed using the *EORTC-QLQ-30 and EQ-5D VAS.*

For the Cohort B participants, the median age of participants was 37 years, with 3 subjects aged 65 years or older. Most subjects were white (88.8%) and more than half were male (63.8%). The majority of the subjects (67.5%) had Stage IV disease at study entry. The median number of cycles of nivolumab was 17 (range 3 to 25); 76% received ≥ 90% of planned dose intensity. At time of analysis, the median duration of follow-up was 8.9 months (range 1.9, 11.7) and the median duration of treatment had not been reached.

At the time of the interim report, 51/80 patients remained on treatment. Of the 29 patients who were off treatment, reasons for discontinuing treatment were:

- 13 due to disease progression
- 4 due to study drug toxicity
- 2 due to subject request (one patient chose to have allogeneic SCT, one patient request due to joint and muscle pain)
- 8 due to other reasons (patients to receive allogeneic SCT n = 3 or ASCT n = 1). One of these patients had achieved CR.
- One was lost to follow-up and one was not reported.

Comment: The joint and muscle pain in the patient who requested cessation of treatment does not appear to have been considered an AE or related to nivolumab despite the association of arthralgia and myalgias/myositis with nivolumab.

BOR could not be determined in 3 subjects. The ORR per IRRC = 53/80, 66.3% (95% CI 54.8, 76.4). Of the 53 responders, 7 had BOR of CR and 46 had BOR of PR. Of the other 27 patients, 18 had BOR of SD.

Table 42. Efficacy results for Cohort B

Efficacy parameter	Result Per IRRC Cohort B (n = 80)
ORR (95% CI)	66.3% (54.8, 76.4)
Number of responders (CR + PR)	53
No with CR	7
No with PR	46
No with SD	18

With a median follow-up of 8.9 months, a number of secondary efficacy measures were immature:

- The median DOR per IRRC was 7.8 months (6.64, NA) although this result is immature with 31/53 responders per IRRC still on treatment and censored at the time of the last tumour assessment. Patients who received subsequent anti-tumour therapy without documented progression were also censored.
- The K-M estimate of median PFS per IRRC was 9.99 months (95% CI 8.41, NA), although 56/80 patients were censored at the time of analysis.
- Overall survival results were immature with median not reached.

Health related quality of life measures had only a small number of responses of after 33 weeks of treatment and during follow-up but mean measures from the responses did not show any decline in QoL during the first 33 weeks nivolumab therapy.

7.4.1.2. Study CA209039

Study CA209039 was a Phase I, open label, multicentre, dose escalation, and multidose study investigating nivolumab as monotherapy and in combination therapy in patients with relapsed or refractory haematological malignancies. The interim study report provided in the submission presents results for 23 patients with relapsed/refractory cHL who were treated with nivolumab monotherapy 3 mg/kg every 2 weeks. Treatment was continued until disease progression, PET-scan confirmed CR, unmanageable drug toxicity, patient choice or for a maximum of 2 years. The results of a sub-group of 15 patients who had received brentuximab vedotin as salvage therapy for relapse following ASCT (the 'ASCT-Brenfailed Group') were presented separately. This group matches Cohort B of Study CA209205 and the proposed target population.

The primary measure of anti-tumour activity was the ORR, with assessment of response by the investigators applying the 'protocol-defined lymphoma response criteria (largely based on the 2007 IWG criteria but with components of the 1999 IWG Criteria) for lymphoma progression to regularly scheduled CT scans. Patients with CR on CT scans that persisted for 4 weeks were to have CR confirmed by PET scan. Following a late protocol amendment, retrospective assessments of response by an independent review panel (IRRC), consisting of 3 radiologists and an oncologist, were performed for scans at all time-points. All management decisions during the study were based on the investigator assessments. Other measures such as duration

of response and time to response were also determined. Secondary or exploratory efficacy measures included progression free survival and overall survival.

Results for the ASCT-BrenFailed Group (n = 15)

Not all results for the ASCT-BrenFailed group were provided separately. The following discussion presents the results for this group as available. Otherwise the results for the group of 23 patients are shown, with this indicated.

For the ASCT-BrenFailed group, the median age was 40 years (range 24 to 54), 10/15 patients were male, 12/15 were White with 2 Black and one 'Other'. Patients were heavily pre-treated: with a median of 5 prior regimens (range 2 to 15) and 87% having received three or more previous treatment regimens for the group of 23 patients.

At the time of the interim analysis of the 15 patients:

- 2 patients were continuing with study drug treatment
- 13 patients had discontinued study drug treatment for the following reasons:
  - 5 patients due to disease progression
  - 2 patients due to study drug toxicity (pancreatitis and MDS)
  - 3 at their own request or for 'other reason'
  - 2 patients had achieved confirmed CR per investigator
  - 1 patient had completed 2 years of therapy.

The median number of doses was 24 (range 6 to 48); 73% received ≥ 90% of planned doses. The K-M estimate of median treatment duration was 12.1 months (95% CI: 3.88, 19.58). The median duration of follow-up was 23.3 months (min, max: 7.3, 27.8) for the 23 patients.

A total of 12/23 cHL patients reported subsequent cancer therapy: 8 were from the cHL ASCT-Brenfailed group (53%) and 4 from the cHL Other group (80%). Seven of the 12 patients had BOR of PR or CR. 6 of the 12 patients underwent SCT (allo-SCT n = 5, ASCT n = 1). At the time of the interim analysis, 3 of these 6 patients had died and 2 had developed GVHD. Other therapies included single agent chemotherapy, multiple agent chemotherapy, radiation, novel agents and investigational agents.

Efficacy results of ORR per IRRC showed an ORR of 60% with 9/15 assessed as responders. All responses (BOR) were PR; there were no patients who achieved CR in the ASCT-Bren Failed group.

Table 43. Study CA209039 ORR and DOR results per IRRC

Efficacy parameter	All patients (n = 23)	ASCT-Bren Failed Group (n = 15)
ORR (CR + PR/23)	61%	60%
No with CR	3	0
No with PR	11	9
No with SD	7	5

The range of duration of response was 1.8 to 24 months. For the ASCT-Bren Failed group, the median duration of response per IRRC was 11.96 months (range 1.9, 23). There were 3/9 (33%) per IRRC responders who had an on-going response at the time of DBL and 3/9 (33%) of responders per IRRC who had a DOR of at least 12 months. The range of duration of response was 1.8 to 23 months. The median duration of response was not reached for the whole group.

Based on the IRRC assessment of PFS, the median PFS for ASCT-Bren Failed was 12.7 months (95% CI, 5.91, N.A) and not reached for all cHL subjects. Overall survival was immature, with median overall survival not reached at DBL, after median follow-up of 23 months.

The results of the studies, as presented, demonstrate biological activity of nivolumab in patients with Hodgkin Lymphoma who have been heavily pre-treated, including by ASCT and brentuximab vedotin. Due to immature results in the main study (Cohort B of Study CA209205), the effect of this on overall survival and progression free survival has yet to be determined. However, the result of an estimated PFS of 12.7 months in the sub-group of 15 patients in Study CA209039 is encouraging.

7.4.1.3. Integrated summary

The evaluator is of the opinion that it is inappropriate to combine the results of the 2 studies, given the differences in the studies described in Section 7.3 above. The main results for this 'integrated group' are therefore summarised in Table 44 (below) together with the results for the individual studies. Duration of follow-up and exposure to nivolumab is also shown for the individual studies. Of note is that in the ASCT-Bren Failed group, the median duration of therapy was reached and that these patients received a median of 24 doses of nivolumab compared to 17 doses for Cohort B.

Table 44. Results for the Integrated population and for the individual study populations

Efficacy parameter	**All patients** (n = 95)	**Study CA 209039** ASCT-Bren Failed Group (n = 15)	**Study CA209205** Cohort B (n = 80)
Median Duration of follow-up, months (range)		23.3 (7.3 to 27.8)	8.9 (1.9 to 11.7).
Median treatment duration[a], months (95% CI)		12.1 (3.88, 19.58)	NA (9.26, NA)
Median number of nivolumab doses (range)		24 (6 to 48)	17 (3 to 35)
Efficacy parameter per IRRC			
ORR (95% CI)	62% (55, 75)	60% (32.3, 83.7)	66.3% (54.8, 76.4)
No with CR (%)	7(7%)	0 (0%)	7 (8.7%)
No with PR	55	9	46
DOR (months)[b]			
Median[a] (95% CI)	8.74 (6.83, NA)	11.96 (1.84, NA)	7.79 (6.64, NA)
Min, Max	0.0, 23.1+	1.8, 23.1+	0.0+, 9.5+
PFS (months)[b]			
Median[a] (95% CI)	12.55 (8.54, NA)	12.65 (5.91, NA)	9.99 (8.41, NA)
OS (months)[b]			

Efficacy parameter	All patients (n = 95)	Study CA 209039 ASCT-Bren Failed Group (n = 15)	Study CA209205 Cohort B (n = 80)
Median[a] (95% CI)	NA (21.13, NA)	NA (15.84, NA)	NA
The symbol + indicates a censored value; a) KM estimate; b) Duration of treatment, PFS and OS results in CA209205 Cohort B were immature with median not reached; OS in CA209039 was immature with median not reached. Duration of response in CA209205 is unstable due to 31/53 patients censored			

7.4.1.4. Summary

The ORR per IRRC of around 60% is consistent across the two studies and indicative of biological activity. The CR rate in both studies was low: 0% in the ASCT-Bren Failed Group of Study CA209039 and 8.7% in Cohort B of Study CA209205. In the 15 patients of the ASCT-Bren Failed group in Study CA209039, with a median follow-up of 23 months, the median duration of response was 11.96 months and the median progression free survival was 12.7 months. The median DOR and PFS for Cohort B of Study CA209205 were 7.79 and 9.99 months respectively, although these results are unstable due to the number of patients censored at the time of the interim analysis. The overall survival results were immature in both studies. In Study CA209039, with median follow-up of 23 months, 4/15 of the ASCT-Bren Failed group had died. In Study CA209205, 3/80 patients from Cohort B had died at median follow-up of 8.9 month.

The results indicate biological activity of nivolumab in this patient population with potential clinically important efficacy but interpretation is limited by the small numbers and the lack of comparator. Other uncertainties related to the results for Study CA209205 include immature results due to limited follow-up and study conduct at two high recruiting sites.

In the absence of a comparator arm, comparison must be made to historyical controls to determine how clinically important these results may be. Generally accepted clinical guidelines provide a list of options in this setting but do not rank them. The sponsor has provided a tabulated summary of published prospective studies of experimental single agent therapies in patients who have relapsed following ASCT for HL. The ORR of around 60% seen with nivolumab compares favourably to these single agents, although it is less than the ORR of 75% reported with brentuximab vedotin. Treatment options for relapsed disease following ASCT and brentuximab vedotin also include allo-SCT, repeat ASCT, re-treatment with brentuximab vedotin, single agent chemotherapy, combination chemotherapy, and radiation therapy. ORRs reported in the literature for different treatment regimens used in this setting range from 4 to 100%, although there appear to be many with reported ORR of 50 to 70%. Responses may, however, be short lived with patients progressing through a sequence of treatment regimens. Recent estimates of median survival for patients receiving one or more of these treatment options consider this to be around 2 years.

Allogeneic stem cell transplant is the most important of the available treatment options as it is potentially curative. However, clinical use has been limited due to low long-term PFS rate of 20% to 30% and high rates of morbidity and treatment-related mortality (20 to 60%). Reduced intensity conditioning (RIC) allo-SCT has been developed in the hope of reducing treatment related mortality without compromising efficacy. A recent small study of RIC allo-SCT reported an overall survival rate of 71% (95% CI 67, 76) at one year and 43% (95% CI 39, 46) at 4 years.

Comparison may also be made to brentuximab vedotin. This was approved by the TGA for use in patients with CD30+ HL who relapsed following ASCT on the basis of early data, as documented in the Australian Public Assessment Report for Brentuximab Vedotin. The registrational study for brentuximab vedotin was an open label, single arm, Phase II study of 102 patients. After

median follow-up of 9 months, an ORR per IRRC of 75% was reported, with a CR of 34% and median duration of objective response of 6.7 months (range 1.2+ to 26.1+ months). This was supported by two dose escalation studies of 42 and 38 patients with cHL that reported ORRs of 40% and 53%. Follow-up results of the pivotal study at 3 and 5 years have since been reported. These found that most progression events occurred early and in patients who did not achieve CR (47/54, 87% of events during the first year occurred in patients with PR or SD). At 3 year follow-up, the estimated PFS per investigator for all patients was 9.3 months. At 5 year follow-up, the overall survival was 41% and the estimated median overall survival was 40.5 months. In comparison, the proposed registrational studies for nivolumab found a lower ORR and much lower CR rate. Despite this, the median PFS was 12 months after 23 months of follow-up, although this was in a group of only 15 patients.

In summary, nivolumab has demonstrated biological activity in patients with relapsed cHL but the clinical relevance of this is uncertain, given the small patient numbers and immature results. The sponsor is asked to provide a discussion of the clinical relevance of nivolumab in the proposed setting with this including all available treatment options. See Question 25: Clinical relevance in Section 11, below.

7.4.2. Part 2: treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after at least two prior therapies in patients who are not candidates for ASCT.

In support of this indication, there are a small number of patients in Study CA209039 who received nivolumab and who had not received prior treatment with ASCT.

Prior ASCT for relapsed or refractory HL was an inclusion criteria for Cohort B in Study CA209205. However, in Study CA209039, the main inclusion criteria was histologically confirmed HL for which the patient had received previous treatment with at least one chemotherapy regimen. Of the 23 subjects enrolled in the cHL expansion of Study CA209039 and treated with nivolumab 3 mg/kg Q2W, 5 patients had not received prior ASCT ('ASCT-naïve') and 3/5 had also not received prior treatment with brentuximab vedotin. Of the 5 ASCT naïve patients, 4 had an objective response to nivolumab, with BOR per IRRC of CR (n = 3), PR (n = 1) and SD (n = 1). Of the 3 patients who had not received prior ASCT or brentuximab vedotin, the BOR per IRRC was CR (n = 1), PR (n = 1) and SD (n = 1).

It is difficult to draw any conclusions given the very small numbers but the results suggest that prior ASCT is not required for nivolumab to demonstrate biological activity in patients with relapsed/refractory HL.

The current TGA approved indications for brentuximab vedotin in HL are:

- Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):
  - following autologous stem cell transplant (ASCT) or
  - following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

According to the sponsor's proposed wording, the second part of the indication would propose nivolumab as an alternative to brentuximab vedotin in patients who have received at least two prior therapies and in whom ASCT is not an option. The efficacy of nivolumab in comparison to brentuximab vedotin in this situation has not been tested according to the materials provided by the sponsor. Only three patients have been described, from Study CA209039, who fit this description of receiving nivolumab in relapsed/refractory HL without prior ASCT or brentuximab vedotin.

Information in support of brentuximab vedotin in this setting is more substantive. The following information is provided in the AusPAR for approval of brentuximab vedotin as a NCE to support the indication of '*following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option'*:

'There were two Phase I single arm open label dose escalation studies (Study 0001 and Study 0002) that enrolled patients with HL that had failed systemic chemotherapy induction or salvage and were ineligible for, refused treatment by or previously had had an ASCT or whom had sALCL. Study 0001 enrolled 42 patients with HL, of whom 9 patients had not received prior ASCT. Study 0002 enrolled 38 patients with HL, of whom 8 patients had not received prior ASCT. The objective response rate in HL patients overall was 40% in Study 0001 and 53% in Study 0002. For the patients from both Study 0001 and 0002 who had not received prior ASCT, the ORR was 30%. The EMA's assessment included a larger dataset of 40 HL patients who had not received prior ASCT (and who were treated at 1.8 mg/kg three weekly), from Studies 0001, 0002 and other sources. In this larger population the ORR was 55% (including 22.5% CR, and also including 20% who went on to SCT)'.[28]

As described in the Background section of this CER (see Section 2 above), a number of small retrospective published audits suggest that brentuximab vedotin is efficacious in this setting outside clinical trials. Patient numbers in these studies ranged from 14 to 30 and the reported objective response rates ranged from 53% to 87.5% and the complete response rate from 30% to 50%.

The information provided by the sponsor to support nivolumab in the setting of relapsed/refractory HL after at least two prior therapies in patients who are not candidates for ASCT is extremely limited. The evaluator does not consider this information adequate to support this part of the proposed indication and recommends that it be removed.

8. Clinical safety

8.1. Overview of safety data

For the evaluation of safety, the sponsor has provided:

- Interim CSR for Study CA209205
- Interim CSR for Study CA209039
- Summary of Clinical Safety (SCS)

In addition, there have been:

- 3 Periodic Safety Update Reports (PSURS, PBRERS) provided to the TGA since approval of nivolumab (dated July 2014 to July 2015; July 2015 to January 2016; and January 2016 to July 2016)
- a review of additional safety concerns provided as part of a Safety Related Request to update the PI.

The first 2 PBRERs and the SRR have been reviewed as part of the clinical evaluation for the indication of advanced renal cell cancer. A Periodic Safety Update Report (PSUR) Review for the PSUR dated July 2015 to Jan 2016, as performed by the TGA, is also available. This review provides information regarding Adverse Event Reports (AERs) in the TGA's Adverse Drug-reaction Reporting System (ADRS) for nivolumab.

8.2. Non-pivotal efficacy studies providing evaluable safety data

Study CA209205 and Study CA209039 are non-pivotal efficacy/safety studies and have been described (see respective studies in Section 7. Clinical efficacy above).

[28] Australian Public Assessment Report (AusPAR) for brentuximab vedotin. Therapeutic Goods Administration (TGA) Canberra, Australia; May 2014.

8.2.1. Study CA209205

The safety analysis for this study included all enrolled patients (Cohorts A, B & C) at the time of database lock for the interim analysis. Safety assessments were based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation or dose modification, select AEs, immune-mediated AEs (IMAEs), and clinical laboratory assessments. Adverse events were assessed 'continuously' throughout the study up to 100 days after study drug discontinuation. SAEs related to the study drug could be reported after 100 days. The AE and laboratory parameters were graded using the National Cancer Institute Common Toxicity Criteria (NCI CTC) v4.0. The percentage of subjects who received immune-modulating concomitant medications for management of AEs was reported. The total duration of all immune-modulating medications (excluding overlaps) for the management of select AE and IMAEs was reported.

8.2.1.1. Assessments as per the Study Protocol

All patients were assessed at screening and regularly during treatment (Day 1 of every cycle). An 'End of treatment' assessment and two Follow-up Visit assessments were also performed: Follow up Visit 1 was 35 ± 7 days after last treatment; Follow up Visit 2 was 80 ± 7 days after last treatment. Assessment of adverse events was described as 'continuous' throughout the study.

Each assessment included:

- targeted physical examination of lymph node regions and abdominal organs
- weight and ECOG status
- measurement of vital signs (BP, HR, temperature and measurement of oxygen saturation at rest and on exertion)
- review of concomitant medications
- adverse event assessment continuously
- laboratory tests: extended local laboratory assessments were to be performed within 72 hours prior to dosing from Cycle 1 through Cycle 5 and every alternate dose thereafter (Cycles 7, 9, 11, 13, and so on) and include: CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. Limited on-study local laboratory assessment should be done within 72 hours prior to dosing beginning at Cycle 6 and every alternate dose thereafter (Cycles 8, 10, 12, 14, and so on) and include: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine. A similar panel was performed at the Follow-up visits: CBC with differential, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH.
- pregnancy test if WOCB age: serum or urine within 24 hours prior to first dose and then at least once every 4 weeks (± 7 days) regardless of dosing schedule.

In addition the following tests were performed less frequently:

- Thyroid function testing TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (± 7 days) from first dose regardless of dosing schedule and at both follow-up visits
- GVHD assessments were performed for subjects who discontinued study therapy by proceeding to allogeneic SCT. To be assessed on Day 100, at 6 months, at 1 year and every one year thereafter from the date of stem cell infusion until the first non-CR after SCT is documented.

As per the study protocol, analyses of AEs were conducted for events reported up to 30 days and up to 100 days (extended follow-up) after the last dose of study medication. Separate analyses were provided for AEs occurring within 30 days and AEs occurring within 100 days.

Comment: According to the description of the reporting of AEs, these were to be reported for up to 100 days post last dose and assessed 'continuously'. No further detail regarding the assessment of AE was described. The final follow-up visit was scheduled at 80 days post-dose. See Question 28: Reporting of AEs in Study CA209205 in Section 11, below.

8.2.2. Study CA209039

The safety analysis included all cHL patients (n = 23) who received at least one dose of nivolumab. The assessment of safety was based on the incidence of adverse events (AEs) including clinical laboratory test abnormalities, serious adverse events (SAEs), adverse events leading to discontinuation, select AEs, and deaths.

Adverse events were to be:

- assessed continuously during the study and for 100 days post last treatment
- evaluated according to the NCI CTCAE Version 4.0
- followed until all treatment-related adverse events have recovered to baseline or are deemed irreversible by the investigator.

8.2.2.1. Assessments as per the Study Protocol

All patients were assessed regularly during treatment (Day 1, Day 8, Day 22 then Week 6 and every 2 weeks thereafter). An End-of-treatment assessment and two Follow-up Visit assessments were also performed: Follow-up Visit 1 was 35 ± 7 days after last treatment; Follow-up Visit 2 was 100 to 120 days after last treatment.

Each assessment included:

- brief physical examination including weight
- ECOG status
- measurement of oxygen saturation at rest and on exertion
- measurement of vital signs (BP, HR, temperature)
- adverse event assessment
- review of concomitant medications
- laboratory tests: chemistry (aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, alkaline phosphatase, lactate dehydrogenase, creatinine, creatine kinase, blood urea nitrogen (BUN), lipase, uric acid, glucose, total protein, albumin, sodium, potassium, chloride, calcium, phosphorus with lipase obtained if amylase was abnormal); haematology: CBC with differential and platelets
- urinalysis: total protein, glucose, blood, leukocyte esterase, specific gravity, pH, and microscopic examination of sediment if blood, protein, or leukocyte esterase are positive on the dip stick
- pregnancy test if WOCB age, serum or urine with this obtained within 24 hours prior to treatment.

In addition the following tests were performed less frequently:

- thyroid function panel, including TSH (if TSH is abnormal then obtain free T3 and free T4), at Day 1 and then at Weeks 8, 16, 24, and every 16 weeks thereafter
- ECG at screening and at end-of-treatment

- adrenocorticotrophic hormone (ACTH) as clinically indicated
- full physical examination at End-of-treatment and Follow-Up Visit 2.

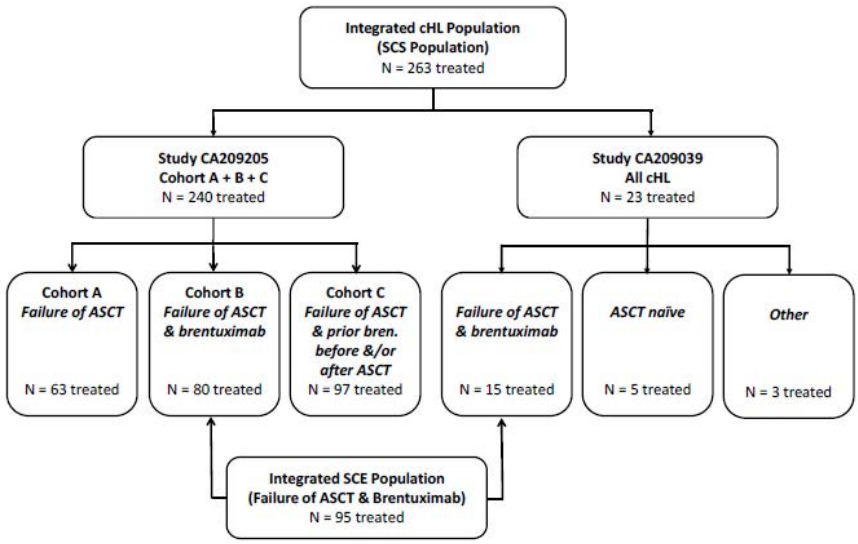
All of the above were performed during the screening process.

The analyses of AEs, as presented in the interim CSR, '*were conducted for events reported up to 100 days (extended follow-up) after the last dose of study medication'*. Only deaths were broken down according to within 30 days or within 100 days of last dose.

8.3. Summary of Clinical Safety

The Summary of Clinical Safety (SCS) presents safety data for 263 cHL subjects from Study CA209205 (Cohort A + B + C, n = 240 patients) + Study CA209039 (all cHL patients, n = 23). This group has been called the 'Integrated cHL Population' by the sponsor and is described as the '*primary population for presentation of safety of nivolumab monotherapy in cHL'*. A less detailed presentation of the patients who had failed ASCT and then brentuximab vedotin prior to nivolumab treatment (n = 95; Study CA209205 Cohort B = 80, Study CA209039 ASCT-Bren Failed = 15) was also provided. This group was called the 'integrated SCE population' and represents the target population for the proposed indication.[29] A summary of the number of patients in each of these groups was provided by the sponsor.

Figure 23. Summary of the cHL groups presented in the Summary of Clinical Safety



According to the SCS report, the primary analyses of AEs, SAEs, and AEs leading to discontinuation for the SCS are based on all treated subjects using a safety window of 30 days after last dose. Additional analyses with extended follow-up (to 100 days post last dose) were also conducted. Analyses of other events of special interest (OESIs) had extended follow-up (100 day window). These were described as including the following categories: demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, pancreatitis, and uveitis.

A comparison of the safety data of the Integrated cHL population and previously submitted nivolumab monotherapy safety data from other tumour types (renal cell carcinoma (RCC), melanoma, and non-small cell lung cancer (NSCLC)) is provided. This is shown in two formats:

- Data from all completed studies that used the intended dose and regimen for nivolumab monotherapy has also been pooled across indications. These results are included in Appendix 5 of the SCS. This includes studies in cHL (Studies CA209205, CA209039), RCC

[29] SCE = Summary of Clinical Efficacy

(Study CA209025), NSCLC studies (Studies CA209057, CA209017, and CA209063) and melanoma studies (Studies CA209037, CA209066, and CA209067 (monotherapy arm only)).

- A comparison across tumour types (RCC, melanoma and NSCLC) is provided in Section 7 of the SCS.

8.4. Patient exposure

Table 45. Exposure to nivolumab in Studies CA209039 and CA209205

	Study CA209039			Study CA209205			
	cHL ASCT Bren-failed[1] N = 15	cHL other N = 8	cHL all N = 23	Cohort A N = 63	Cohort B[1] N = 80	Cohort C N = 97	Cohort A + B + C N = 240
Number of doses received							
mean	25.3	19.3	23.2	11.1	16.1	6.4	10.9
median	24	13	18	11	17	6	10
min, max	6, 48	7, 47	6, 48	1, 24	3, 25	1, 14	1, 25
Median duration of treatment, months (95% CI)	12.09 (3.88, 19.58)	5.78 (2.99, 18.63)	8.18 (5.29, 15.87)	NA	NA (9.26, NA)	NA (5.52, NA)	NA
No on treatment at time of analysis	2	1	3	54	51	90	199
Cumulative dose (mg/kg)							
mean	75.1	56.8	68.7	32.8	47.9	20	32.3
median	68.7	39	54	31	50.9	18	29.7
min, max	8, 138	21, 137	18, 138	3, 73.6	9, 75.8	2.9, 40.9	2.9, 75.8
Relative dose intensity							
> 110%	0	0	0	1 (1.6)	0	0	1 (0.4)
90 ≤ 110%	11 (73.7)	7 (87.5)	18 (78.3)	54 (85.7)	61 (76.3)	83 (85.6)	198 (83)
70 ≤ 90%	4 (26.7)	1 (12.5)	5 (21.7)	6 (9.5)	16 (20.0)	12 (12.4)	34 (14.2)
50 ≤ 70%	0	0	0	2 (3.2)	3 (3.8)	2 (2.1)	7 (2.9)
1) target population							

Table 46. Duration of follow-up in Studies CA209039 and CA209205

	Study CA209039			Study CA209205			
	cHL ASCT Bren-failed N = 15	cHL Other N = 8	cHL all N = 23	Cohort A N = 63	Cohort B N = 80	Cohort C N = 97	Cohort A+B+C N = 240
mean follow-up	20.8	22.6		5.3	8.6	2.9	5.4
median follow-up (months)	21.9	24	23.3	5.1	8.9	2.8	5.1
range	11.2, 27.6	22.9, 25.9	7.3, 27.8	1, 11.1	1.9, 11.7	0.3, 6.9	0.3, 11.7
Note follow-up is defined as Time between date of first dose and last known date alive (for subjects who are alive) or death (months)							

According to an appendix of the SCS, 1991 patients have been exposed to nivolumab monotherapy in company-sponsored clinical trials. This pooled population is made up of the integrated cHL population (n = 263), RCC population (n = 406), melanoma population (n = 787) and NSCLC population (n = 535). The median number of doses received was 10 (range 1 to 65) and 77% of patients received more than 4 doses. The median cumulative dose was 30 mg/kg (range 0.5 to 195).

The SCS provides the following comparison across tumour types. Note that the integrated cHL population (including patients from Cohort A and C of Study CA209205) is used in this comparison.

Table 47. Cumulative dose and exposure to nivolumab across tumour types

	cHL N = 263	RCC N = 406	Melanoma N = 787	NSCLC N = 535
NUMBER OF DOSES RECEIVED				
MEAN (SD)	11.9 (8.41)	19.2 (16.25)	15.4 (10.99)	12.0 (12.49)
MEDIAN (MIN - MAX)	10.0 (1 - 48)	12.0 (1 - 65)	12.0 (1 - 45)	6.0 (1 - 52)
CUMULATIVE DOSE (MG/KG)				
MEAN (SD)	35.45 (24.074)	57.72 (49.025)	46.20 (33.144)	36.05 (37.388)
MEDIAN (MIN - MAX)	30.15 (2.9 - 137.8)	36.03 (0.5 - 195.1)	36.00 (3.0 - 135.0)	18.04 (1.4 - 156.0)
RELATIVE DOSE INTENSITY				
>= 110%	1 (0.4)	3 (0.7)	3 (0.4)	0
90% TO < 110%	216 (82.1)	330 (81.3)	681 (86.5)	447 (83.6)
70% TO < 90%	39 (14.8)	64 (15.8)	88 (11.2)	75 (14.0)
50% TO < 70%	7 (2.7)	8 (2.0)	13 (1.7)	11 (2.1)
< 50%	0	1 (0.2)	2 (0.3)	2 (0.4)
DURATION OF THERAPY (MONTHS)				
MIN, MAX (A)	0.03, 23.36	0.03, 29.60+	0.03, 20.30+	0.03, 23.95+
MEDIAN (95% CI) (B)	12.222 (12.090, 20.501)	5.536 (5.060, 6.932)	5.815 (5.092, 6.669)	2.727 (2.300, 3.023)
N OFF TRT/N TREATED (%)	65/263 (24.7)	335/406 (83.5)	495/787 (63.4)	456/535 (85.2)
OTHER STATISTICS				
MEAN	5.367	8.847	6.967	5.405
STANDARD DEVIATION	4.1322	7.7990	5.2302	6.0416
> 3 MONTHS (%)	181 (68.8)	294 (72.4)	518 (65.8)	246 (46.0)
> 6 MONTHS (%)	97 (36.9)	198 (48.8)	379 (48.2)	165 (30.8)
> 9 MONTHS (%)	45 (17.1)	157 (38.7)	308 (39.1)	114 (21.3)
> 12 MONTHS (%)	10 (3.8)	119 (29.3)	175 (22.2)	91 (17.0)
TOTAL EXPOSURE (P-Y)	124.5	328.3	500.2	277.8

Nivolumab monotherapy treatment groups from the following studies are included in the disease categories: cHL: CA209205, CA209039 (cHL patients); RCC: CA209025; Melanoma: CA209037, CA209066, CA209067; NSCLC: CA209063, CA209017, CA209057.
P-Y = person-years of exposure.
(A) Symbol + indicates a censored value.
(B) Median computed using Kaplan-Meier method.

Comment: Patients with relapsed/refractory cHL who are treated with nivolumab monotherapy appear to receive this treatment for longer compared to patients with other tumour types treated with nivolumab monotherapy. This is shown by the

median number of doses of 18 received by cHL patients in Study CA209039 (with a median of 24 doses for the ASCT-Bren Failed group) and 17 by Cohort B patients from Study CA209205, compared to a median of 12 doses for patients with melanoma and RCC, and 6 for patients with NSCLC) and by the Kaplan Meier estimates of median duration of therapy for Cohort B and the cHL population of Study CA209039 (shown in Table 47, above). However, the median number of doses received by the cHL population in the sponsor's comparison table above (the 'integrated cHL' population) was 10, reflecting the inclusion of Study CA209205 Cohort A (median number of doses of 11) and Cohort C (median number of doses of 6). Of note is that only 24.7% of the integrated cHL population were off-treatment at the time of the safety analysis, compared to over 60 to 80% for other tumour types. Inclusion of the Cohort A and C patients, who do not match the target population and who have immature results at the time of the analysis, renders interpretation of the safety results presented by the sponsor difficult. The sponsor is asked to repeat this analysis using the SCE population (the ASCT-Bren Failed group from Study CA209039 and Cohort B from Study CA209205) and using updated safety information regarding Cohort B. See Question 26: Updated safety analysis of adverse events (inclusion of Cohorts A and C from Study CA209205 in the safety analysis) in Section 11, below.

8.5. Evaluator comments on the sponsor's presentation of safety

The evaluator has some concerns regarding the sponsor's presentation of safety, in particular, the grouping together of cHL patients with widely varying nivolumab exposure and follow-up.

The proposed treatment with nivolumab is open ended, with treatment continued until disease progression or unacceptable toxicity. The Exposure-Response Safety analysis provided in the dossier has indicated that the occurrence of more serious AEs is related to duration of treatment (see above Figure 12. K-M plot of probability of Grade 3+ AEs by duration of treatment.).

In Study CA209039, an interim analysis was performed after a minimum follow-up of 18 months. At the time of this analysis, only 3 patients were still receiving nivolumab treatment, the median number of nivolumab doses received was 18 for all patients, and 24 for the ASCT-BREN failed group, and the median duration of follow-up was 23 months. Enrolment into the different cohorts of Study CA209205 commenced at different timepoints and occurred at different rates. An interim analysis was performed after a minimum follow-up of 6 months for the Cohort B patients. At the time of the analysis there was in Cohort B 51/80 (64%) patients still receiving treatment, the median number of nivolumab doses was 17 and the median duration of follow-up was 8.9 months. For Cohort A and C, with a median follow-up of 5 and 3 months respectively, over 80% of patients were still receiving nivolumab treatment.

The evaluator would interpret these results as indicating that in clinical use of nivolumab in the proposed population of patients with cHL who have progressive disease following ASCT and then brentuximab vedotin, and in whom treatment is continued until disease progression or unacceptable toxicity, most patients will continue on nivolumab treatment for more than 17 doses and that many will continue for more than 24 doses. The safety results of Cohort A and C from Study CA209205 (and even Cohort B), may therefore be considered 'immature'. The evaluator notes that the sponsor has acknowledged this in the SCS with the statement: '*Compared with CA209205 Cohort B and CA209039 all cHL, the safety profile for subjects in CA209205 Cohort A or Cohort C may not be as adequately characterized at these database locks due to the shorter extent of follow up in these cohorts.'*

Given that Cohort A + C together numerically make up 61% of the *Integrated cHL Population*, inclusion of these patients in the safety analysis risks 'dilution' of the safety results with underestimation of AEs and over-estimation of the safety of nivolumab in the cHL population.

Comparison of the frequency of reported AEs by PT for the integrated cHL population compared to the Study CA209039 and Cohort B population shows that the frequency of AEs (all grade and Grade 3 or 4) is noticeably lower in the integrated cHL population. This may be the effect of small numbers in CA209039 and Cohort B, but it is the evaluator's opinion that the difference is more likely due to dilution by the inclusion of a large number of patients from Cohort A + C of Study CA209205 who received relatively few doses of nivolumab. The rates reported for Study CA209039 and Cohort B may be more representative of rates likely to be experienced by the target population (see Question 26: Updated safety analysis of adverse events and Question 27: Updated comparison across tumour types in Section 11, below).

The evaluator also notes that the main presentation of AEs in the SCS is only for those AEs that occurred within 30 days of last does of nivolumab, rather than the extended reporting period of 100 days provided in the individual studies. The extended reporting period is used to capture immune related AEs that have been described as occurring up to 6 months after the last dose of nivolumab.

To ensure that the safety aspects described will be more generalisable to the target population, the following presentation of safety provided by the evaluator will be largely based on that of Study CA209039, Cohort B from Study CA209205 and the integrated SCE population. Information from the integrated cHL, and Cohorts A + C from Study CA209205 will be provided separately where relevant. The integrated cHL population, with this including Cohorts A and C of Study CA209205, will be referred to, particularly for the description of rare events.

8.6. Dose delays or interruption of nivolumab treatment

8.6.1. Study CA209039

There were 34 dose delays involving 11 patients, of whom 9 were in the ASCT-Bren Failed group. Of the dose delays, 17 were due to non-haematological toxicity and 17 were for 'other reasons'. Non-haematologic toxicity included rash, cough/viral illness, vomiting, pain, thumb infection, sinusitis, flu, lung infection, bronchospasms, pneumonia, muscle pain and Grade 2 lipase elevation. 'Other' reasons included personal or administrative reasons (visits rescheduled).

Three subjects, all from the cHL ASCT-Bren Failed group reported infusion interruptions due to Grade 1 or 2 hypersensitivity reactions (n = 2) and infusion administration difficulties (infusion line disconnected) (n = 1). Only 1 subject reported recurrent infusion interruption for hypersensitivity reaction.

8.6.2. Study CA209205

Cohort B:

- There were 97 delayed doses out of 1208 administered doses (8%). These occurred in 49/80 patients (60%), with 27 patients experiencing more than one delay. The majority (84.5%) of delays lasted less than 14 days. The most common reasons for dose delay were reported as AEs (53/97, 54.6%) and 'other' (44/97, 45.4%)
- 5 patients required infusion interruption; reasons given were hypersensitivity reaction (n = 1) and other (n = 4)
- 4 (5.0%) subjects required infusion rate reduction; reported reasons were hypersensitivity reactions (n = 2), infusion administration issues (n = 1), and 'other' (n = 2).

Cohorts A and C:

- There were 51 delayed doses out of 1159 administered doses (4.4%). These occurred in 40/160 patients (25%), with 9 patients experiencing more than one delay. The majority (38/51, 75%) of delays lasted less than 14 days. The most common reasons for dose delay were reported as AEs (27/51, 53%) and 'other' (23/51, 45%)

- 5 patients required infusion interruption; reasons given were hypersensitivity reaction (n = 3), infusion administration issues (n = 1), and other (n = 1)
- 4 subjects required infusion rate reduction for the following reported reasons: hypersensitivity reactions (n = 2), infusion administration issues (n = 1), and 'other' (n = 1).

8.7. Adverse events

The following presentation of AEs shows those reported during the extended follow-up period of 100 days where possible. This is preferred by the evaluator over follow-up to 30 days as it has been recognised that immune mediated AEs may occur up to 6 months after the last dose of nivolumab.

As discussed above, the groups presented by the evaluator are the study population from Study CA209039, Cohort B from Study CA209205 and the integrated SCE population. Cohorts A and C of Study CA209205 are also referred to so as to provide a more complete description of rare events.

Comparison is made in the SCS to other groups that have received nivolumab monotherapy:

- Pooled population:
  - An appendix of the SCS provides 'Integrated Nivolumab Monotherapy Safety Data' with this describing a population of 'all treated subjects'. The group is defined in the appendices as: '*Nivolumab treatment group consists of Nivolumab monotherapy treatment group from Studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209205 and CA209039 (cHL patients).'* This group is referred to as the pooled population by the evaluator.
- Tumour types:
  - The SCS provides a comparison of AEs in the cHL population to other populations according to tumour type (RCC, melanoma, NSCLC).

8.7.1. All adverse events (irrespective of relationship to study treatment)

Table 48. Summary of the most common AEs reported in 20% or more patients in Studies CA209039 or CA209205 for the reporting period of 100 days

	Study CA209039 **all cHL (N = 23)**		Study CA209205 **Cohort B (N = 80)**		SCE population[1] **(30 days, N = 95)**	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
System Organ Class (%)						
Preferred Term (%)						
Total number with an AE	23 (100)	13 (56.5)	79 (98.8)	32 (40.0)	94 (98.9)	79 (30.0)
General disorders and administration site	19 (82.6)	2 (8.7)	51 (63.8)	2 (2.5)	65 (69.4)	3 (3.2)
Fatigue	12 (52.2)	1 (4.3)	29 (36.3)	0	35 (36.8)	1 (1.1)
Pyrexia	11 (47.8)	0	25 (31.3)	0	33 (34.7)	1 (1.1)
Respiratory, thoracic and mediastinal	18 (78.3)	2 (8.7)	39 (48.8)	3 (3.8)	52 (54.7)	7 (2.7)

	Study CA209039 **all cHL (N = 23)**		Study CA209205 **Cohort B (N = 80)**		SCE population[1] **(30 days, N = 95)**	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Cough	14 (60.9)	0	22 (27.5)	0	32 (33.7)	0
Nasal congestion	6 (26.1)	0	0	0	8 (8.4)	0
Gastrointestinal disorders	16 (69.6)	4 (17.4)	48 (60.0)	3 (3.8)	56 (58.9)	5 (5.3)
Diarrhoea	11 (47.8)	1 (4.3)	22 (27.5)	0	28 (29.5)	1 (1.1)
Nausea	7 (30.4)	0	19 (23.8)	0	22 (23.2)	0
Vomiting	7 (30.4)	0	13 (16.3)	1 (1.3)	15 (15.8)	1 (1.1)
Infections and infestations	16 (69.6)	3 (13.0)	53 (66.3)	8 (10.0)	63 (66.3)	8 (8.4)
Upper respiratory tract infections	6 (26.1)	0	19 (23.8)	0	23 (24.2)	1 (1.1)
Nasopharyngitis	0	0	16 (20.0)	0	16 (16.8)	0
Skin and subcutaneous tissue disorders	16 (69.6)	3 (13.0)	38 (47.5)	3 (3.8)	49 (51.6)	3 (3.2)
Rash	10 (43.5)	0	17 (21.3)	2 (2.5)	24 (25.3)	2 (2.1)
Pruritus	9 (39.1)	0	18 (22.5)	0	23 (24.2)	0
Blood and lymphatic disorders	15 (65.2)	7 (30.4)	16 (20.0)	9 (11.3)	22 (23.2)	9 (9.5)
Thrombocytopaenia	9 (39.1)	4 (17.4)	2 (2.5)	0	8 (8.4)	1 (1.1)
Lymphopenia	5 (21.7)	3 (13.0)	0	0	1 (1.1)	0
Investigations	15 (65.2)	3 (13.0)	34 (42.5)	12 (15.0)	43 (45.2)	14 (14.7)
ALT increased	5 (21.7)	0	4 (5.0)	2 (2.5)	6 (6.3)	2 (2.1)
Metabolism and nutrition disorders	14 (60.9)	2 (8.7)	21 (26.3)	3 (3.8)	27 (28.4)	3 (3.2)
Hyperglycaemia	9 (39.1)	0	8 (10.0)	1 (1.3)	12 (12.6)	1 (1.1)
Hypokalaemia	5 (21.7)	0	6 (7.5)	0	7 (7.4)	0
Musculoskeletal and connective tissue disorders	12 (52.2)	1 (4.3)	34 (42.5)	4 (5.0)	42 (44.2)	3 (3.2)
Back pain	5 (21.7)	1 (4.3)	10 (12.5)	2 (2.5)	12 (12.6)	1 (1.1)
Arthralgia	4 (17.4)	0	18 (22.5)	0	20 (21.1)	0
Nervous system disorders	10 (43.5)	0	31 (38.8)	2 (2.5)	37 (38.9)	1 (1.1)
Headache	5 (21.7)	0	9 (11.3)	1 (1.3)	11 (11.6)	1 (1.1)
Peripheral neuropathy	5 (21.7)	0	10 (12.5)	0	15 (15.8)	0
Renal and urinary disorders	7 (30.4)	1 (4.3)	0	0	0	0
Endocrine disorders	5 (21.7)	0	13 (16.3)	0	16 (16.8)	0
Injury, poisoning and	5 (21.7)	0	18 (22.5)	0	20 (21.1)	0

	Study CA209039 **all cHL (N = 23)**		Study CA209205 **Cohort B (N = 80)**		SCE population[1] **(30 days, N = 95)**	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
procedural complications						
Infusion related reaction	1	0	16 (20.0)	0	17 (17.9)	0
Hypersensitivity	1	0				
Psychiatric disorders	5 (21.7)	0	13 (16.3)	0	13 (13.7)	0
1) The integrated SCE population is comprised of 15 patients from CA209039 and all Cohort B patients from CA209205; the reporting period for AEs for patients in the SCE population was 30 days.						

Comment: Almost all of all grade AEs and Grade 3 or 4 AEs by PT occur more frequently in the Study CA209039 population, compared to Cohort B. This may reflect the greater duration of treatment in these patients.

8.7.1.1. Study CA209205 (100 days)

Cohort B (n = 80)

Any causality, any grade AEs were reported in 98.8% of subjects, with Grade 3 or 4 AEs reported in 40.0% of subjects. There was one Grade 5 AE, the PT was Multi-organ failure.

The most frequently reported (≥ 20%) all-causality, any grade AEs are shown in the table above. These included: fatigue (36.3%); pyrexia (31.3%); cough (27.5%); diarrhoea (26.3%); nausea, upper respiratory tract infection (23.8%); pruritus (22.5%); arthralgia, rash (21.3%), infusion related reaction and nasopharyngitis (20.0%).

The most frequently reported (> 2%) Grade 3 or 4 all-causality AEs were: lipase increased (6.3%), neutropaenia (5.0%), abdominal pain (2.5%), ALT increased (2.5%), amylase increased (2.5%), anaemia (2.5%), AST increased (2.5%), dyspnoea (2.5%), lung infection (2.5%), and rash (2.5%).

Cohorts A + B + C (n = 240)

Any grade AEs were reported in 92.9% subjects, with Grade 3 or 4 AEs reported in 27.5% of subjects. There were 3 Grade 5 AEs, the PTs were Multi-organ failure, Atypical pneumonia (n = 1), and Dyspnoea (n = 1).

8.7.1.2. Study CA209039 (100 days)

All 23 cHL patients reported at least on AE within 100 days of last dose. Grade 3 or 4 AEs were reported in 13 (56.5%) patients. There were no Grade 5 AEs reported within 100 days of last dose.

The most frequently reported (≥ 20%) all-causality, any grade AEs are shown in Table 48, above. These included: cough (60.9%); fatigue (52.2%); diarrhoea and pyrexia (47.8%); rash (43%); hyperglycaemia, pruritus, thrombocytopaenia (39%); nausea, vomiting (30%), upper respiratory tract infection, nasal congestion (26%), headache, peripheral neuropathy, back pain, hypokalaemia, lymphopaenia, and increased ALT (21.7%).

The most common Grade 3 or 4 AEs were thrombocytopaenia in 4 (17.4%) subjects and lymphopenia in 3 (13%) subjects. All other Grade 3 or 4 AEs occurred in 1 or 2 subjects.

8.7.1.3. Integrated SCE population (30 days, n = 95)

The SCE population is those patients who were treated with nivolumab monotherapy following failure of brentuximab vedotin after ASCT. This is the target population for the main part of the

proposed indication. It is comprised of 15 patients from Study CA209039 and all 80 patients from Cohort B of Study CA209205.

All causality AEs of any grade were reported in 98.9% of subjects, with Grade 3 or 4 AEs reported in 41.1% of subjects. There was one Grade 5 event; the PT was Multi-organ failure.

The most frequently reported any grade AEs (≥ 20% of subjects) by PT are shown in the Table 48, above. The most common were: fatigue (36.8%), pyrexia (34.7%) and diarrhoea (29.5%).

The most common Grade 3 or 4 AEs were lipase increased in 6 (6.3%) patients and neutropaenia in 4 (4.2%) subjects (with one report of Grade 3 or 4 febrile neutropaenia). All other Grade 3 or 4 AEs occurred in 1 or 2 subjects.

8.7.1.4. Integrated cHL population (30 days, n = 263)

All causality AEs of any grade were reported in 93.5% of subjects, with Grade 3 or 4 AEs reported in 30.0% of subjects.

The most frequently reported any grade AEs (≥ 20% of subjects) were fatigue (27.8%), pyrexia (24.3%), diarrhoea (23.2%), and cough (20.5%).

The most frequently reported Grade 3 or 4 AEs (≥ 2% of subjects) were lipase increased (3.8%), and neutropaenia (2.3%).

There were 3 Grade 5 AEs; the PTs were Multi-organ failure, Atypical pneumonia (n = 1), and Dyspnoea (n = 1).

Comment: The frequency of all cause AEs by PT (all grade and Grade 3 or 4) is noticeably lower in the integrated cHL population compared to the Study CA209039 and Cohort B populations.

8.7.1.5. Pooled results for all patient who have received nivolumab monotherapy

The SCS reports that 1991 patients have received nivolumab monotherapy in company sponsored studies (Studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209205 and CA209039 (integrated cHL population from Studies CA209039 and CA209205). The presentation was of events reported between first dose and 30 days after last dose of study therapy.

All causality AEs of any grade were reported in 97.2% of subjects, with Grade 3 or 4 AEs reported in 43.1% of subjects and Grade 5 events reported in 112/1991 (5.6%).

The most frequently reported any grade AEs (≥ 10% of patients) were fatigue (39.4%), nausea (24.6%), cough (24.3%), diarrhoea (23.4%), constipation (19.2%), dyspnoea (18.7%), vomiting (14.9%), pyrexia (16.1%), asthenia (12.8%), arthralgia (15.2%), back pain (13.7%), pruritus (17.9%), rash (17.0%), headache (13.7%), decreased appetite (19.9%), and anaemia (14.1%). Infusion related reactions were reported in 3.8%.

The most common Grade 3 or 4 AEs (≥ 1.0%) were fatigue (2.7%), asthenia (1.2%), pain (1.4%), diarrhoea (1.7%), abdominal pain (1.1%), dyspnoea (2.7%), pneumonia (2.3%), pleural effusion (1.4%), pulmonary embolism (1.2%), back pain (2.0%), hypertension (1.6%), hypercalcaemia (1.1%), hyperglycaemia (1.6%), hyponatraemia (1.8%), ALT increased (1.7%), AST increased (1.6%), lipase increased (1.7%), GGT increased (1.0%), anaemia (3.3%) and malignant neoplasm progression (3.2%).

Grade 5 events included:

- 5 reports (0.3%) of pneumonia
- 3 reports (0.2%) each of multi-organ failure, respiratory failure, and cardiorespiratory arrest
- 2 reports each of 'physical health deterioration', sudden death, dyspnoea, and pulmonary embolism

- One report each of performance status decreased, death, gastrointestinal disorder, haemoptysis, atypical pneumonia, cerebral haemorrhage, subarachnoid haemorrhage, neutropaenia, completed suicide, SVC syndrome, aortic aneurysm rupture, malignant melanoma, non-small cell lung cancer, lung neoplasm malignant, head injury, toxicity to various agents, cardiac failure, myocardial infarction, and cardiopulmonary failure
- 70 reports of malignant neoplasm progression.

Comment: The pattern of all grade and Grade 3 or 4 AEs appears similar across the cHL populations and in comparison to the cHL populations to the pooled population with over 90% of patients experiencing an AE of any grade, around 40% experiencing a Grade 3 or 4 AE and the most commonly reported AEs being fatigue, cough, diarrhoea and pyrexia. The rates of these common events were, however, highest in the Study CA209039 population. Grade 5 AEs (excluding malignant neoplasm progression) were reported in 2% of the pooled population but only 1% of the integrated SCE population and integrated cHL population. Interpretation of this is difficult due to the small numbers of cHL patients.

8.7.1.6. Results across tumour types

The following summary is provided in the SCS for individual tumour types.

Table 49. Summary of nivolumab safety across tumour types

	cHL N = 263	RCC N = 406	Melanoma N = 787	NSCLC N = 535
NUMBER OF SUBJECTS WHO DIED (%)	12 (4.6)	181 (44.6)	251 (31.9)	339 (63.4)
WITHIN 30 DAYS	4 (1.5)	19 (4.7)	57 (7.2)	66 (12.3)
WITHIN 100 DAYS	5 (1.9)	56 (13.8)	151 (19.2)	181 (33.8)
STUDY DRUG TOXICITY	1 (0.4)	0	1 (0.1)	2 (0.4)
AEs, all grades	246 (93.5)	397 (97.8)	768 (97.6)	524 (97.9)
AEs, Grade 3-4	79 (30.0)	216 (53.2)	319 (40.5)	244 (45.6)
MOST FREQUENTLY REPORTED AEs (≥ 20% of subjects, all grades)				
FATIGUE	73 (27.8)	195 (48.0)	328 (41.7)	189 (35.3)
PYREXIA	64 (24.3)	67 (16.5)	114 (14.5)	76 (14.2)
DIARRHOEA	61 (23.2)	96 (23.6)	223 (28.3)	86 (16.1)
COUGH	54 (20.5)	128 (31.5)	148 (18.8)	154 (28.8)
NAUSEA	45 (17.1)	115 (28.3)	213 (27.1)	117 (21.9)
PRURITUS	44 (16.7)	75 (18.5)	182 (23.1)	56 (10.5)
RASH	39 (14.8)	64 (15.8)	176 (22.4)	60 (11.2)
CONSTIPATION	24 (9.1)	92 (22.7)	155 (19.7)	111 (20.7)
BACK PAIN	21 (8.0)	87 (21.4)	104 (13.2)	60 (11.2)
DYSPNOEA	19 (7.2)	94 (23.2)	102 (13.0)	157 (29.3)
DECREASED APPETITE	16 (6.1)	93 (22.9)	132 (16.8)	156 (29.2)
DRUG-RELATED AEs, all grades	188 (71.5)	319 (78.6)	609 (77.4)	362 (67.7)
DRUG-RELATED AEs, Grade 3-4	42 (16.0)	76 (18.7)	108 (13.7)	59 (11.0)
MOST FREQUENTLY REPORTED DRUG-RELATED AEs (≥ 10% of subjects, all grades)				
FATIGUE	42 (16.0)	134 (33.0)	230 (29.2)	105 (19.6)
INFUSION RELATED REACTION	32 (12.2)	13 (3.2)	20 (2.5)	9 (1.7)
DIARRHOEA	29 (11.0)	50 (12.3)	135 (17.2)	44 (8.2)
NAUSEA	29 (11.0)	57 (14.0)	108 (13.7)	64 (12.0)
RASH	27 (10.3)	41 (10.1)	133 (16.9)	45 (8.4)
PRURITUS	23 (8.7)	57 (14.0)	145 (18.4)	34 (6.4)
DECREASED APPETITE	8 (3.0)	48 (11.8)	63 (8.0)	66 (12.3)
ASTHENIA	6 (2.3)	18 (4.4)	59 (7.5)	56 (10.5)
ALL SAEs, all grades	55 (20.9)	194 (47.8)	319 (40.5)	263 (49.2)
DRUG-RELATED SAEs, all grades	26 (9.9)	47 (11.6)	64 (8.1)	42 (7.9)
ALL AEs LEADING TO DC, all grades	11 (4.2)	72 (17.7)	91 (11.6)	99 (18.5)
DRUG-RELATED AEs LEADING TO DC, all grades	11 (4.2)	31 (7.6)	41 (5.2)	32 (6.0)

MedDRA Version: 18.0; CTC version 4.0; Includes events reported between first dose and 30 days after last dose of study therapy.
Nivolumab monotherapy treatment groups from the following studies are included in the disease categories: cHL: CA209205, CA209039 (cHL patients); RCC: CA209025; Melanoma: CA209037, CA209066, CA209067; NSCLC: CA209063, CA209017, CA209057.

Comment: The integrated cHL population in the above table appears different from that of the other tumour types, with rates of Grade 3 or 4 AEs (all cause and drug related) and SAEs noticeably lower in the integrated cHL population. Comparison to the reported rates in the individual cHL studies), show that the rates of the most commonly reported AEs are higher in the cHL population, although the rates of Grade 3 or 4 AEs and SAEs are similar. Deaths occurred more commonly with the other tumour types.

Table 50. Comparison of AEs across tumour types and Studies CA209039 and CA209205

	CA209039 N = 23	**Cohort B CA209205** N = 80	**RCC** N = 406	**Melanoma** N = 787	**NSCLC** N = 535
Total subjects with an event (%)					
All Cause, all grades AEs	23 (100)	79 (98.8)	397 (97.8)	768 (97.6)	524 (97.9)
All cause, Grade 3 or 4 AEs	13 (56.5)	32 (40.0)	216 (53.2)	319 (40.5)	244 (45.6)
Drug-related AEs, Grade 3 or 4	5 (21.7)	20 (25.0)	76 (18.7)	108 (13.7)	59 (11.0)
Discontinuations due to AEs	2 (13.3)	3 (3.8)	72 (17.7)	91 (11.6)	99 (18.5)
SAEs, all grades	8 (40)	20 (25)	194 (47.8)	319 (40.5)	263 (49.2)
Deaths	5 (21.7)	3 (3.8)	181 (44.6)	251 (31.9)	339 (63.4)
Within 30 days of last dose	0	1(1.3)	19 (4.7)	57 (7.2)	66 (12.3)
Within 100 days of last dose	0	1(1.3)	56 (13.8)	151 (19.2)	181 (33.8)
Attributed to nivolumab toxicity	0	1 (1.3)	0	1 (0.1)	2 (0.4)
Most frequently reported AEs, all grades					
Fatigue	12 (52.2)	29 (36.3)	195 (49.0)	328 (41.7)	189 (35.3)
Pyrexia	11 (47.8)	25 (31.3)	67 (16.5)	114 (14.5)	76 (14.2)
Diarrhoea	11 (47.8)	22 (27.5)	96 (23.6)	223 (28.3)	86 (16.1)
Cough	14 (60.9)	22 (27.5)	120 (31.5)	148 (18.0)	154 (28.0)
Nausea	7 (30.4)	19 (23.8)	115 (28.3)	213 (27.1)	117 (21.9)
Pruritus	9 (39.1)	18 (22.5)	75 (18.5)	182 (23.1)	56 (10.5)
Rash	10 (43.5)	17 (21.3)	64 (15.8)	176 (22.4)	60 (11.2)

Comparison of safety to the safety in other tumour types is particularly important given the apparent difference in the pharmacokinetics of nivolumab in patients with cHL, where reduced clearance results in higher nivolumab exposure (according to $C_{avg,ss}$). The sponsor is requested to provide updated information, with this including patients from Cohort A and C after a longer period of follow-up. See Question 27: Updated comparison across tumour types in Section 11, below.

The rate of infusion related reactions is considerably higher in the cHL population compared to other tumour types. This is discussed further below.

8.7.2. Drug-related adverse events (adverse drug reactions)

Table 51. Summary of the most common AEs in Studies CA209039 and CA209205 (any grade reported in 2 or more patients and any reports of Grade 3 or 4) for the extended period of 100 days

System organ class (%)	Study CA209039 All cHL (n = 23)		CA209205 Cohort B (n = 23)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Preferred term (%)				
Total number with an AE	19 (82.6)	5 (21.7)	72 (90.0)	20 (25.0)
General disorders and administration site	9 (39.1)	2 (8.7)	32 (40.0)	0
Fatigue	3 (13.0)	0	20 (25.0)	0
Pyrexia	3 (13.0)	0	11 (13.8)	0
Respiratory, thoracic and mediastinal disorders	3 (13.0)	1 (4.3)	13 (16.3)	2 (2.5)
Cough	1 (4.3)	0	3 (3.8)	0
Pneumonitis	1 (4.3)	1 (4.3)	2 (2.5)	1 (1.3)
Dyspnoea	1 (4.3)	0	3 (3.8)	1 (1.3)
Gastrointestinal disorders	9 (39.1)	2 (8.7)	30 (37.5)	2 (2.5)
Diarrhoea	3 (13.0)	0	8 (10)	0
Nausea	3 (13.0)	0	10 (12.5)	0
Vomiting	1 (4.3)	0	6 (7.5)	0
Abdominal pain	0	0	6 (7.5)	2 (2.5)
Constipation	0	0	5 (6.3)	0
Colitis	1 (4.3)	1 (4.3)	0	0
Stomatitis	1 (4.3)	1 (4.3)	0	0
Gastrointestinal inflammation	1 (4.3)	1 (4.3)	0	0
Hepatobiliary disorders	0	0	2 (2.5)	1 (1.3)
Autoimmune hepatitis	0	0	1 (1.3)	1 (1.3)
Infections and infestations	1 (4.3)	0	10 (12.5)	1 (1.3)
Respiratory tract infection	1 (4.3)	0	3 (3.8)	0

System organ class (%)	Study CA209039 All cHL (n = 23)		CA209205 Cohort B (n = 23)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Pneumonia	0	0	1 (1.3)	1 (1.3)
Skin and subcutaneous tissue disorders	6 (26.1)	0	23 (28.8)	2 (2.5)
Rash	4 (17.4)	0	13 (16.3)	1 (1.3)
Pruritus	3 (13.0)	0	8 (10)	0
Blood and lymphatic disorders	9 (39.1)	3 (13.0)	7 (8.8)	4 (5.0)
Neutropaenia	1 (4.3)	0	7 (8.8)	4 (5.0)
Thrombocytopaenia	5 (21.7)	1 (4.3)	1 (1.3)	0
Anaemia	0	0	2 (2.5)	0
Lymphopenia	3 (13.0)	1 (4.3)	0	0
Investigations	6 (26.1)	1 (4.3)	19 (23.8)	9 (11.3)
Lipase increased	3 (13.0)	1 (4.3)	6 (7.5)	4 (5.0)
Amylase increased	0	0	4 (5.0)	2 (2.5)
AST increased	1 (4.3)	0	4 (5.0)	2 (2.5)
ALT increased	1 (4.3)	0	3 (3.8)	2 (2.5)
Metabolism and nutrition disorders	5 (21.7)	0	6 (7.5)	0
Hypercalcaemia	2 (8.7)	0	0	0
Decreased appetite	1 (4.3)	0	2 (2.5)	0
Hyperglycaemia	1 (4.3)	0	4 (5.0)	0
Hypokalaemia	0	0	1 (1.3)	0
Musculoskeletal and connective tissue disorders	3 (13.0)	0	21 (26.3)	2 (2.5)
Back pain	0	0	3 (3.8)	1 (1.3)
Myalgia	2 (8.7)	0	6 (7.5)	0
Arthralgia	1 (4.3)	0	11 (13.8)	0
Eye disorders	0	0	6 (7.5)	0
Dry eye	0	0	2 (2.5)	0

System organ class (%)	Study CA209039 All cHL (n = 23)		CA209205 Cohort B (n = 23)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Nervous system disorders	2 (8.7)	0	15 (18.8)	1 (1.3)
Headache	0	0	2 (2.5)	0
Peripheral neuropathy	2 (8.7)	0	3 (3.8)	0
Vascular disorders	0	0	4 (5.0)	0
Hot flush	0	0	2 (2.5)	0
Hypertension	0	0	2 (2.5)	0
Renal and urinary disorders	0	0	0	0
Endocrine disorders	3 (13.0)	0	11 (13.8)	0
Hypothyroidism	2 (8.7)	0	6 (7.5)	0
Primary hypothyroidism	0	0	3 (3.8)	0
Thyroiditis	0	0	2 (2.5)	0
Injury, poisoning and procedural complications	2 (8.7)	0	16 (20.0)	0
Infusion related reaction	1 (4.3)	0	16 (20.0)	0
Psychiatric disorders	0	0	5 (6.3)	0

Treatment Related Grade 5 AEs:

- There were no Grade 5 AEs in Study CA209039.
- There was one treatment related Grade 5 AE in Cohort B of Study CA209205, the PT was Multi-organ failure; there were 2 other treatment related Grade 5 AEs in Cohort A and C of Study CA209205, the PTs were Multi-organ failure (n = 1, Cohort B), Atypical pneumonia (n = 1), and Dyspnoea (n = 1).

Comment: The proportion of AEs assessed as drug related differs across the 2 studies with a considerably smaller proportion of AEs reported as drug related by the investigators in Study CA209039 (see Table 52, below). This is relevant to the descriptions provided by the sponsor for 'select AEs' (see Question 32: Select AEs, drug related or not; the investigators of Study CA209205 and Study CA209039 in Section 11, below).

Table 52. Comparison of the proportion of AEs by PT assessed as drug related in Studies CA209039 and CA209205

	Study CA209039, All cHL (N = 23)		Study CA209205, Cohort B (N = 80)	
	Any Grade, any causality, n	Any grade drug related, n (%*)	Any Grade, any causality, n	Any grade drug related, n (%)[1]
Preferred Term				
Total number with an AE	23	19 (82.6)	79	72 (91)
Fatigue	12	3 (25)	29	20 (68)
Pyrexia	11	3 (27)	25	11 (44)
Cough	14	1 (7)	22	3 (13)
Diarrhoea	11	3 (27)	22	8 (36)
Nausea	7	3 (42)	19	10 (53)
Vomiting	7	1 (14)	13	6 (46)
1) % refers to the proportion of all AEs by that PT assessed as 'Drug related'				

8.7.2.1. Drug related AEs in Study CA209205 (100 days)

Cohort B (n = 80)

Any grade drug related AEs were reported in 90.0% of subjects, with Grade 3 or 4 AEs reported in 25% of subjects. There was one Grade 5 AE.

Frequently reported (≥ 2 patients) drug related, any grade AEs are shown in Table 52, above. The most common of these were: fatigue (25%); infusion related reaction (20%) and rash (16.3%).

Grade 3 or 4 drug related AEs occurred in 20 patients. The most commonly reported Grade 3 or 4 AEs by PT for the extended follow-up period were: lipase increased (n = 4, 5.0%) and neutropaenia (n = 4, 5.0%). All other Grade 3 or 4 AEs occurred in 1 or 2 patients.

There was one drug related Grade 5 AE, this had the reported PT of multi-organ failure.

Cohorts A + B + C (n = 240)

Any drug related grade AEs were reported in 70.4% subjects, with Grade 3 or 4 AEs reported in 15.4% of subjects. There were 3 Grade 5 AEs.

The most frequently reported (> 10%) drug related any grade AEs were: fatigue (16.3%), diarrhoea (10.8%) and nausea (10.8%).

Grade 3 or 4 drug related AEs occurred in 37 patients. The most commonly reported Grade 3 or 4 AEs by PT for the extended follow-up period were: lipase increased (n = 6, 2.5%), amylase increased (n = 4, 1.7%) and neutropaenia (n = 4, 1.7%). All other Grade 3 or 4 AEs occurred in 1 or 2 patients.

There were 3 Grade 5 AEs, the PTs were Multi-organ failure (from Cohort B), Atypical pneumonia (n = 1), and Dyspnoea (n = 1).

8.7.2.2. Drug related AEs in Study CA209039 (100 days, n = 23)

Any drug related grade AEs were reported in 19/23 (82.6%) of patients, with Grade 3 or 4 AEs reported in 5/23 (21.7%) of patients. There were no Grade 5 AEs reported within 100 days of last dose.

The most frequently reported (≥ 2 patients) drug related any grade AEs are shown in the Table 52, above. The most commonly reported were: fatigue (13%); pyrexia (13%); diarrhoea (13%); nausea (13%); rash (17.4%) and pruritus (13%).

There were 10 Grade 3 or 4 drug related AEs reported in 5 patients. According to a table of the CSR, each Grade 3 or 4 AE was reported in one patient and were: lipase increased, lymphopenia, thrombocytopaenia, leukopenia, pancreatitis, colitis, stomatitis, GIT inflammation, pneumonitis and myelodysplastic syndrome.

8.7.2.3. Drug related AEs in the Integrated SCE population (30 days, n = 95)

Any grade drug related AEs were reported in 89.5% of subjects, with Grade 3 or 4 AEs reported in 24.2% of subjects. There was one Grade 5 AE.

The most commonly reported (> 10%) drug related, any grade AEs were: fatigue (22.1%); infusion related reaction (17.9%), rash (16.8%), pyrexia (14.7%), arthralgia (12.6%), nausea 11 (11.6%), pruritus (10.5%), and diarrhoea (10.5%).

Grade 3 or 4 drug related AEs occurred in 23 patients. The most commonly reported Grade 3 or 4 drug related AEs by PT in the 30 day reporting period were: lipase increased (n = 5, 5.3%) and neutropaenia (n = 4, 4.2%). All other Grade 3 or 4 AEs occurred in 1 or 2 patients.

There was one drug related Grade 5 AE, this was a patient in Cohort B with the reported PT of multi-organ failure.

8.7.2.4. Drug related AEs in the Integrated cHL population (30 days, n =263)

Drug related AEs of any grade were reported in 188/263 (71.5%) of subjects, with Grade 3 or 4 AEs reported in 16% of subjects. There were 3 Grade 5 events (all in Study CA209205). The PTs were Multi-organ failure (from Cohort B), Atypical pneumonia (n = 1), and Dyspnoea (n = 1).

The most frequently reported any grade AEs (≥ 10% of subjects) were fatigue (16%), infusion related reaction (12.2%), pyrexia (9.1%), diarrhoea (11%), and nausea (11%).

Reported Grade 3 or 4 AEs were rash in 2 patients, fatigue, infusion related reaction and diarrhoea in one patient each.

8.7.2.5. Drug related AEs: Pooled results for all patients who have received nivolumab monotherapy

The SCS reports that 1991 patients have received nivolumab monotherapy in company sponsored studies (Studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209205 and CA209039 (cHL patients). The presentation was of events reported between first dose and 30 days after last dose of study therapy.

Drug related AEs of any grade were reported in 1478/1991 (74%) of subjects, with Grade 3 or 4 AEs reported in 285 (14.3%) and Grade 5 events reported in 5 (0.3%).

The most frequently reported any grade drug-related AEs (≥ 5% of patients) were fatigue (25.7%), pyrexia (6.1%), asthenia (7.0%), nausea (13.0%), diarrhoea (13.0%), constipation (5.3%), vomiting (5.7%), arthralgia (6.2%), pruritus (13.0%), rash (12.4%), hypothyroidism (5.9%), anaemia (4.2%). cough (4.8%), and dyspnoea (4.2%). Infusion related reactions were reported in 3.7% (compared to 17.9% in the integrated SCE population).

The most common Grade 3 or 4 AEs (≥ 1.0%) were fatigue (1.4%), diarrhoea (1.1%), ALT increased (1.0%), and lipase increased (1.2%).

Grade 5 events were:

- One report each of multi-organ failure, dyspnoea, neutropaenia, pneumonia, and atypical pneumonia.

Comment: Note that the presentation for the pooled population is for AEs occurring within 30 days compared to within 100 days for the cHL populations. The patterns of AEs reported, according to the most frequent, were similar except for infusion reactions. These were more commonly reported in the integrated SCE cHL population.

8.7.2.6. Drug related AEs: Results across tumour types

The SCS provides a comparison to separate tumour types (see Table 49. Summary of nivolumab safety across tumour types, above).

Comment: The sponsor has provided two comparisons of the rates of AEs in a cHL population to rates reported in other populations. The cHL population used for the comparison is the 'integrated cHL' population that includes all patients from Study CA209039 and all patients from Study CA209205, including patients from Cohort A and C. One comparison is the integrated cHL population to a 'pooled population' of 1991 patients who have been treated with nivolumab monotherapy in company sponsored studies (Studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209205 and CA209039). This pooled population includes the integrated cHL population. The other comparison provided is the integrated cHL population compared to patients who have received nivolumab monotherapy in company sponsored studies according to tumour type. The integrated cHL population compares favourably to both the pooled population and the individual tumour types, with rates of AEs (all causality and drug related, SAEs) either similar or lower.

However, as described above, at the time of the interim analysis, the patients from Cohort A and Cohort C had a relatively low exposure to nivolumab but make up 60% of the integrated cHL population. Comparison to other cHL populations is, therefore, shown in the tables below.

Table 53. Comparison of cHL populations to the Pooled Population

	CA209039 N = 23	**Cohort B, CA209205** N = 80	**Integrated SCE[1]** N = 95	**Integrated cHL[1]** N = 263	**Pooled population[1]** N = 1991
All cause AEs, all grades (%)	100	98.8	98.9	93.5	97.2
All cause AEs, Grades 3/4 (%)	56.5	40	30	30	43.1
All cause AEs, Grade 5 (%)	0	1.25	1.1	1.14	5.6
Drug-related AEs, all grades (%)	82.6	90	89.5	71.5	74
Drug-related AEs, Grades 3, 4 (%)	21.7	25	24.2	16.0	14.3
Drug-related AEs, Grade 5 (%)	0	1.25	1.1	1.14	0.3
1) the presentation for the SCE, integrated cHL and the pooled populations is for AEs occurring within 30 days of last dose compared to within 100 days for the Study CA209039 and Cohort B populations					

The cHL populations with greater exposure to nivolumab (Study CA209039, Cohort B and the integrated SCE populations), do not compare as favourably to the pooled population and demonstrate higher rate of drug-related AEs, all grades and Grade 3 or 4.

Table 54. AE rates of cHL population compared to separate tumour types (30 day reporting period)

	CA209039 N = 23	Cohort B CA209205 N = 80	Integrated SCE N = 95	Integrated cHL N = 263	RCC N = 406	Melanoma N = 787	NSCLC N = 535
Median number of doses	18	17	Not available[1]	10	12	12	6
AEs (%)							
All cause AEs, all grades	100	98.8	98.9	93.5	97.8	97.6	97.9
All cause AEs, Grades 3/4	56.5	40	30	30	53.2	40.5	45.6
Drug-related AEs, all grades	82.6	90	89.5	71.5	78.6	77.4	67.7
Drug-related AEs, Grades 3/4	21.7	25	24.2	16.0	18.7	13.7	11
SAEs, all grades	35	25	27.4	20.9	47.8	40.5	49.2
SAEs, drug-related, all grades	13	6.3	8.4	9.9	11.6	8.1	7.9
Deaths within 100 days	0	1.3	1.1	1.9	13.8	19.2	33.8

Note: Study CA209039, in the 100 day reporting period. 1) The evaluator was unable to locate this in the dossier. However the median number of doses for the ASCT-Bren Failed group in Study CA209039 was 24 and the median number of doses in Cohort B was 18.

Comparison of the integrated SCE population to patients with other tumour types suggest that patients with relapsed/refractory cHL are likely to continue on nivolumab treatment for longer, are more likely to have drug related AEs (all grades and Grade 3 or 4) but appear to have similar rates of drug related SAEs. Comparison of the rates of deaths is limited by small numbers in the HL populations.

8.7.3. Deaths

Table 55. Summary of deaths in cHL populations

	Study CA209039	Study CA209205 Cohort B	Study CA209205 Cohorts A + C	Integrated SCE	Integrated cHL
n (%)	N = 23	N = 80	N = 160	N = 95	N = 263
Deaths	5 (21.7)	3 (3.8)	4 (2.5)	7 (7.4)	12 (4.6)
disease progression	2 (8.7)	1 (1.3)	3 (1.9)	3 (3.2)	6 (2.3)
nivolumab toxicity	0	0	1 (0.6)	0	1 (0.4)
unknown	0	1 (1.3)	0	1 (1.1)	1 (0.4)

	Study CA209039	Study CA209205 Cohort B	Study CA209205 Cohorts A + C	Integrated SCE	Integrated cHL
other	3 (13.0)	1 (1.3)	0	3 (3.2)	4 (1.5)
No who died within 30 days of last dose	0	1 (1.3)	3 (1.9)	1 (1.1)	4 (1.5)
disease progression	0	0	2 (1.25)	0	2 (0.8)
nivolumab toxicity	0	0	1 (0.6)	0	1 (0.4)
unknown	0	0	0	0	0
other	0	1 (1.3)	0	1 (1.1)	1 (0.4)
No who died within 100 days of last dose	0	1 (1.3)	4 (2.5)	1 (1.1)	5 (1.9)
disease progression	0	0	3 (1.9)	0	3 (1.1)
nivolumab toxicity	0	0	1 (0.6)	0	1 (0.4)
unknown	0	0	0	0	0
other	0	1 (1.3)	0	1 (1.1)	1 (0.4)

SCE population = 15 patients from Study CA209039 + all 80 Cohort B patients

Integrated cHL population = 23 patients from Study CA209039 + 240 patients from Cohorts A + B + C

8.7.3.1. Study CA209205

There were 12 subjects who died during the study, including 5 subjects who died after enrolment but did not receive study drug. Of the 7 patients who received nivolumab, 3 were in Cohort B. Of the 7 deaths, the cause was attributed to disease progression in 4 patients, to 'Other' in one patient, to 'study drug toxicity' in one patient and the cause of death in one patient was unknown. Narratives were not provided for patients whose deaths were attributed to disease progression, except for three patients who also had SAEs reported. A total of 6 narratives were, therefore, provided and are summarised below.

There were 4 deaths within 30 days of the last dose of nivolumab. Narratives were available for 3 of these patients:

- One death that occurred within 30 days of nivolumab administration was attributed to study drug toxicity. This patient (from Cohort A) developed rapidly progressing respiratory failure on Day 13, when the second dose of nivolumab was scheduled to be administered. The patient was hospitalised and required invasive ventilation due to ongoing deterioration the following day. Treatments included broad spectrum antimicrobials (including treatment for *Pneumocystis jiroveci*) and immunosuppressive doses of corticosteroids. Sputum sample on Day 16 was positive for *Pneumocystis jiroveci*. The patient continued to deteriorate and died from multiple system failure on Day 30. Death was attributed to atypical pneumonia and this was assessed by the investigator as related to study drug. According to the narrative, '*Post database lock, the site changed this event's relationship to study therapy to not-related'.*

Comment: This patient's death is likely to be due to *Pneumocystis jiroveci* infection that did not respond to treatment. This is an infection seen in immunocompromised patients and not currently recognised as an adverse reaction associated with nivolumab. However, according to the most recent PSUR, there have been 15 SAEs of *Pneumocystis jiroveci* infection in patients receiving nivolumab in sponsor trials and lymphopenia has been reported in some populations of patients (for example, 21.7% of patients in Study CA209039).

- One patient (from Cohort C) received 11 cycles of nivolumab treatment (168 days). The treatment was complicated by an SAE of pleural effusion requiring hospitalisation and drainage on Day 151. Nivolumab treatment was discontinued on Day 182 due to disease progression. On Day 185, the patient was hospitalised with dyspnoea that was reported as an SAE and considered related to study drug by the investigator. The outcome of the dyspnoea was reported as fatal on Day 187. However, the cause of death was attributed to disease progression by the investigator. No further details regarding this progression or dyspnoea were provided in the narrative. The baseline disease was reported to be mediastinal.

Comment: Immune mediated pneumonitis and pleural effusion cannot be excluded as a possible cause of dyspnoea. Pneumonitis is a recognised immune related AE associated with nivolumab. Pleural effusion is not recognised currently but it is notable for the number of reports from post-marketing sources (35 reports in the 6 month period January to July 2016 according to the most recent PBRER). There were also 4 reports of pleural effusion as an SAE in Cohorts A + C of Study CA209205. An immune-related condition does not appear to have been considered for this patient and the patient did not receive treatment with corticosteroids.

- One patient (in Study CA209205, Cohort B) was hospitalised with multisystem organ failure (MSOF) 3 days after dose 14 of nivolumab (Day 190). The patient was treated with corticosteroids, broad spectrum antimicrobials and supportive care including invasive ventilation and vasopressor infusions. Complications at the time included *C. difficile* negative diarrhoea, superficial bleeding gastric ulcers (requiring massive transfusion), abnormal LFTs, elevated amylase, pancytopenia, acute kidney injury and DIC. 'Stress-dose' steroids were given. The patient continued to deteriorate and died from MSOF on Day 199. The MSOF was assessed as related to study drug by the investigator. An autopsy showed a new diagnosis of Epstein Barr Virus positive peripheral T-cell lymphoma. No further details regarding this were provided. According to the narrative: '*Post database lock, the site changed the event of multi-organ failure to EBV positive peripheral-T cell lymphoma, with onset of Day 190, and considered to be not related to study therapy*'

Comment: No detail is provided regarding the autopsy diagnosis. MSOF has been reported in other patients receiving nivolumab but EBV positive peripheral T-cell lymphoma may also present with a fulminant process, including MSOF. The investigator changed the assessment of 'drug related' to 'not drug related' on the basis of the autopsy result.

One death occurred 95 days after the last dose of nivolumab

- One patient was hospitalised 7 days after the first dose of nivolumab with dehydration secondary to vomiting. The patient received two further doses of nivolumab and then discontinued treatment after re-staging CT scan showed disease progression. The patient died from disease progression on Day 124.

There were two deaths occurring more than 100 days after the last dose of nivolumab:

- In one patient death from disease progression occurred 111 days after the last dose of nivolumab. In this patient an infusion related reaction occurred with the first dose but not with the subsequent 3 doses. After the second dose of nivolumab, the patient developed a

'lung infection' that was assessed as related to nivolumab and treated with antibiotics for 14 days and then with a course of corticosteroids. After the fourth dose, disease progression was diagnosed and nivolumab treatment discontinued. The patient was hospitalised with pneumonia on Day 134 and was treated with broad spectrum antibiotics. The patient died from this illness (pneumonia in the setting of relapsed cHL) 20 days later.

Comment: There is insufficient detail to exclude a persistent immune related pneumonitis as a contributor to this patient's death.

- In one death, occurring more than 200 days after the last dose of nivolumab, the cause was 'unknown'. This patient (from Study CA209205 Cohort B) received three cycles of nivolumab. The subsequent course was complicated by abnormal LFTs attributed to the study drug and treated with corticosteroids. This was closely followed by Grade 3 dyspnoea requiring hospitalisation that was reported as pneumonitis on the basis of the CT appearance and considered related to study drug. This was treated by increased doses of corticosteroids and broad spectrum anti-microbial drugs. The patient improved and discontinued from the study (42 days after the last dose of nivolumab and Day 75 of the study). During steroid taper, the patient was again hospitalised with dyspnoea and respiratory failure and improved on increased steroid doses. The patient's death was reported some time later (Day 304) with the cause unknown. The patient was still receiving treatment with methylprednisolone and prednisolone at the time of death.

Comment: according to the SCS, this patient was 'lost to follow-up'. According to the narrative provided in the CSR, the patient was known to be on immunosuppressive drugs at the time of death. The patient appears to have had a prolonged and recurrent immune related illness. It is possible that this contributed to the patient's death.

8.7.3.2. Study CA209039

At database lock for the interim analysis, 5 (21.7%) of all cHL subjects treated with nivolumab had died: 2 from disease progression and 3 for reason other (complications of allo-SCT n = 2; pulmonary compromise n = 1). All 5 deaths occurred > 100 days after the last dose of nivolumab and following subsequent therapy. None of the deaths were assessed as related to study drug. Four of the 5 patients had undergone allo-SCT prior to death.

From the narratives provided:

- One patient achieved PR and discontinued nivolumab and study to undergo allo-SCT at Week 29. The patient was followed for survival and reported to die from disease progression at Week 92.
- One patient achieved SD but subsequently developed progressive disease and discontinued treatment at Cycle 7. The patient received subsequent therapy (chemotherapy and immunotherapy) and was reported to die 390 days after last nivolumab dose.
- One patient achieved PR and discontinued nivolumab and study at Week 11 (Day 80), to undergo allo-SCT, with this performed at Week 17 (Day 120). The patient subsequently developed GVHD (Grade 2 severity) requiring hospitalisation and treatment with methylprednisolone at 2mg/kg. Corticosteroids were continued until Day 192. On Day 455, the patient was hospitalised with a *Pseudomonas* Grade 4 lung infection and died some 10 days later. GVHD was reported to be ongoing at the time of death.
- One patient achieved PR with nivolumab discontinued on Day 150 due to disease progression, with the last dose given on Day 118. The patient subsequently had an allo-SCT performed on Day 211. The patient is reported to have died from complications of the allo-SCT 220 days later. No further details are provided in the narrative.
- One patient continued nivolumab treatment after initial disease progression and achieved PR. After a last dose of nivolumab on Day 106, the patient discontinued for the study to undergo an allo-SCT on Day 116. Shortly after the allo-SCT, the patient was hospitalised

with febrile neutropaenia. On Day 148, the patient was hospitalised with GVHD and was commenced on immune-suppressive doses of corticosteroids (methylprednisolone and prednisolone. The patient was discharged on sirolimus and budesomide for GVHD – this was subsequently changed to mycophenolic acid. On Day 158, the patient was hospitalised with encephalitis that responded to foscarnet. On Day 187, the patient was hospitalised with MSSA bacteraemia, cryptosporidium infection and thrombotic microangiopathy. The patient progressively deteriorated with respiratory and renal failure and died on Day 223. The patient's death was attributed to complications of the allo-SCT.

Comment: There were 5 patients in Study CA209039 who discontinued study drug to undergo allo-SCT. At the time of the interim analysis, 4 had died from complications of the allo-SCT. Two of these 4 patients had developed GVHD.

8.7.4. Serious adverse events

Table 56. Summary of SAEs (30 day reporting period) in cHL populations

Total subjects with an event (%)	Study CA209039 n = 23	Study CA209205 Cohort B n = 80	Integrated SCE n = 95	Integrated cHL n = 263
Any grade	8 (40)	20 (25)	26 (27.4)	55 (20.9)
Grade 3 or 4	5 (33.3)	10 (12.5)	15 (15.8)	33 (12.5)
Grade 5	0	1 (1.3	1 (1.1)	3 (1.1)

Additional detail is provided below regarding these patients under the heading of the relevant study. The Integrated SCE and Integrated cHL populations are not separately presented given that the patients are derived from the two studies.

8.7.4.1. Study CA209205

Cohort B: All Causality SAEs

There were 29 all-causality SAEs of any grade were reported in 20/80 (25.0%) of subjects.

- The most frequently reported SAEs (≥ 2% of subjects) were pyrexia (3.8%), arrhythmia (2.5%), infusion related reaction (2.5%), malignant neoplasm progression (2.5%), meningitis (2.5%), and pneumonia (2.5%).
- There were 18 all causality Grade 3 or 4 SAEs reported in 10/80 (12.5%) of subjects. No PTs were reported in more than 1 subject except for malignant neoplasm progression (2 subjects, 2.5%). The SAEs by PT reported in single patients were: pneumonia, lung infection, dyspnoea, meningitis, pyrexia, generalised oedema, arrhythmia, pericardial effusion, cardiac failure, gastrointestinal stromal tumour, hypercalcaemia, syncope, rash, maculopapular rash, platelet count decreased, osteonecrosis, febrile neutropaenia and embolism.
- 1 (1.3%) subject experienced a Grade 5 SAE of multi-organ failure. This subject is described above.

Cohort B: Drug-related SAEs

There were 5 drug related SAEs of any grade were reported in 5/80 (6.3%) of subjects. None of these were described as Grade 3 or 4 and one was described as Grade 5 (MSOF event described above). The SAEs reported as Grade 1 or 2 were infusion related reactions in 2 patients and meningitis and pyrexia in single patients.

Cohorts A + C: All Causality SAEs

There were 33 all causality SAEs of any grade were reported in 27/160 (17%) of subjects.

- The most frequently reported SAEs (≥ 2 subjects) were: pneumonia (n = 2), pleural effusion (n = 4), pneumonitis (n = 3), infusion related reaction (n = 3).
- There were 22 all-causality Grade 3 or 4 SAEs reported in 16/160 (10%) of subjects. Only one Grade 3 or 4 SAE was reported in more than one patient: pneumonia (n = 2). Grade 3 or 4 SAES in single patients were: parainfluenza infection, *pneumocystis jiroveci* infection, respiratory tract infection, lung disorder, pneumothorax, pericardial effusion, pyelonephritis, diarrhoea, infusion related reaction, erysipelas, dehydration, glucose tolerance impaired, rash, ALT increased, pain in extremity, trachea-oesophageal fistula, abortion induced.
- 2 patients experienced Grade 5 SAEs; these are described above.

Cohorts A + C: Drug-related SAEs

A table provided drug-related SAEs for a reporting period of 100 days. There were 18 patients in whom 23 all grade SAEs were reported. Of these, 8 were Grade 3 or 4 SAEs and 2 were Grade 5 SAEs. All drug-related Grade 3 or 4 SAEs were reported in single patients and included diarrhoea, infusion related reaction, pneumonia, pyelonephritis, pericardial effusion, increased ALT, glucose tolerance impaired and rash.

Comment: Narratives for 51 reported SAEs were provided. In general, the evaluator agreed with the attribution of related versus not related, within the limits of the information provided (noting that some narratives included only sketchy information). There were, however, a number of cases of non-specific illnesses for which other causes were not identified and in which a possible immune-mediated cause did not appear to be considered. These included cases of pneumonitis/respiratory failure/pneumonia, pleural effusions, pericardial effusion, meningitis/encephalitis, general deterioration. This resulted in delayed (or no) administration of immunosuppressive therapy and may have resulted in worse patient outcomes (see also the summary of the narrative of the second patient listed in Section 8.7.3. Deaths, above). Note that investigators were provided with training in the recognition and management of immune mediated AEs and that the Investigator's Brochure also provided descriptions and guidelines for management.

Other cases were informative in that they showed 1) that it was not unusual for patients to have more than one type of immune-mediated adverse event (both sequentially and simultaneously) and 2) that immune-mediated adverse event could have a prolonged and relapsing course even with immunosuppressive therapy and cessation of nivolumab treatment.

Some summaries of narratives demonstrating lack of recognition of possible immune related AEs are [not reproduced in this document].

8.7.4.2. Study CA209039

All causality

A total of 15 SAEs of all causality within 100 days of last dose were reported in 8 (35%) subjects. Of these, 12/15 SAEs were Grade 3 or 4, involving 7 patients. There were no Grade 5 events reported. Most SAEs were reported in 1 subject each: mycoplasma pneumonia, skin infection, lymph node pain (Grade 1 or 2), thrombotic microangiopathy, encephalitis, pancreatitis, small bowel obstruction, post-operative fever (Grade 1 or 2), abnormal LFTs, myelodysplastic syndrome, acute kidney injury and haemoptysis. The study drug was discontinued in the patients in whom pancreatitis and MDS were reported. Febrile neutropaenia and GVHD were reported as SAEs in 2 patients each. In one patient, GVHD was Grade 1 or 2, in the other it was Grade 3 or 4.

Drug related

Of the above SAEs, 3 were reported as related to study drug: 1 subject with lymph node pain (Grade 2); 1 subject with pancreatitis and 1 subject with MDS (both Grade 3; which resulted in discontinuation from the study).

Comment: The evaluator has read the narratives provided and agrees with the investigator's attribution within the limits of the information provided. Of note is that a number of patients underwent other treatments for cHL (including allo-SCT) during the reporting period of 100 days. Summaries of some of the narratives are [not provided in this document].

8.7.4.3. Pooled results for all patients who have received nivolumab monotherapy

The SCS reports that 1991 patients have received nivolumab monotherapy in company sponsored studies (Studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209205 and CA209039 (integrated cHL population from Studies CA209039 and CA209205). The presentation was of events reported between first dose and 30 days after last dose of study therapy.

Drug related SAEs of any grade were reported in 179/1991 (9%) of subjects, with Grade 3 or 4 AEs reported in 113 (5.7%) and Grade 5 events reported in 5 (0.3%).

No single AE by PT had a frequency of ≥ 2% of patients. The most frequently reported any grade AE were pneumonitis (1.2%), diarrhoea (0.6%), infusion related reaction (0.5%), pyrexia (0.5%), colitis (0.4%), hyperglycaemia (0.4%) fatigue (0.3%) and adrenal insufficiency (0.3%).

Grade 3 or 4 drug related AEs reported in more than 2 patients were: pneumonitis (n = 14, 0.7%), diarrhoea (n = 10, 0.5%), hyperglycaemia (n = 7, 0.4%), colitis (n = 6, 0.3%), adrenal insufficiency (n = 4, 0.3%), dyspnoea (n = 3, 0.2%), fatigue (n = 3, 0.2%), acute kidney injury (n = 3, 0.2%), tubulointerstitial nephritis (n = 3, 0.2%), ALT increased (n = 3, 0.2%), and autoimmune hepatitis (n = 3, 0.2%).

Grade 5 events by PT were: neutropaenia, atypical pneumonia, pneumonia, multiple organ failure, and dyspnoea.

A table of the SCS provides another means of assessing the impact of SAEs in the pooled population.

Comment: The data regarding the pooled population is from study appendices.

Table 57. SAEs and nivolumab monotherapy, All treated subjects

	Monotherapy data integrated across indications (n = 1991)	
	n	%
SAEs, total	831	41.7
SAEs, fatal	173	8.7
Hospitalisation or prolonged hospitalisation	735	36.9
Life-threatening	29	1.5
Cancer	34	1.7
Disability/incapacity	2	0.1

8.7.5. Discontinuation due to adverse events

Additional detail is provided below regarding these patients under the heading of the relevant study. The Integrated SCE and Integrated cHL populations are not separately presented given that the patients are derived from the two studies.

8.7.5.1. Study CA209205

The frequency of all-causality, any grade AEs leading to discontinuation of study therapy in all cohorts were reported in 3.8% subjects.

Cohort B

There were 3 patients reported to have discontinued treatment due to AEs in Cohort B. The AEs were: Grade 3 or 4 autoimmune hepatitis, Grade 3 or 4 AST/ALT increased and Grade 5 MSOF (described above).

Comment: According to the description of participant flow in the CSR, there were 4 patients in Cohort B who discontinued treatment due to nivolumab toxicity. The sponsor is asked to explain this discrepancy (see Question 29: Discontinuations due to nivolumab toxicity in Study CA209205 in Section 11, below).

Cohort A + C

There were 6 patients reported to discontinue treatment due to AEs in Cohort A + C. The AEs by PT reported in these patients were: Grade 1 or 2 autoimmune nephritis, Grade 1 or 2 pneumonitis, Grade 1 or 2 pleural effusion, Grade 3 or 4 pneumonia, Grade 3 or 4 pericardial effusion, Grade 3or 4 hepatitis, and Grade 5 atypical pneumonia (described above).

8.7.5.2. Study CA209039

There were 2 (8.7%) subjects who discontinued treatment due to AEs of pancreatitis (Grade 3) and MDS (Grade 3), both of which were considered drug-related. Both patients were in the ASCT-Bren Failed cohort.

8.7.6. Immune mediated adverse events

8.7.6.1. Terminology of 'select adverse events', 'immune mediated adverse events' and 'other events of special interest (OESI)'

Evaluator comments on the presentation of immune mediated adverse events

The major safety concern with nivolumab is immune related adverse events. Understanding the descriptions of these events, as provided in the sponsor's documents, is hampered by the terminology used. The presentations of AEs that have a possible immune mediated cause provided in the sponsor's interim CSRs include the sub-groups of 'select AEs' and 'immune mediated adverse events' (IMAEs). Study CA209205 also includes 'other events of special interest (OESI)' and Study CA209039 describes 'other IMAES of special interest'. The nivolumab PI refers to 'immune related' conditions in the Precautions section (for example immune mediated pneumonitis) and 'select adverse reactions' in the Adverse Events section. The SCS has described 'select AEs' and 'OESI'.

In short, the sub-groups appear to be described by (more detailed definitions are provided below):

- Select AEs/select adverse reactions: possible immune related AEs occurring within 30 days (Study CA209205) or 100 days (Study CA209039) of last dose of nivolumab that may or may not require immunosuppressive therapy
- IMAEs: possible immune related AEs occurring within 100 days of last dose of nivolumab and that do require immunosuppressive therapy, except for endocrine events
- OESI: possible immune-related AES that are rare but have previously been reported with nivolumab and that occur within 100 days of last dose of nivolumab

- Other IMAEs of special interest: these seem to be OESI but with the added requirement that the event required immunosuppressive therapy.

The reports of these AEs are not determined prospectively by the investigators but are determined through searches of all reported AEs using multiple PTs (as selected by the sponsor). However, the investigator's brochure gives advice regarding the recognition and management of immune related AEs.

The evaluator is concerned that the use of multiple different terms adds unnecessary complexity to the descriptions of these AEs, risks obscuring their common aetiology as immune-mediated and makes determining the frequency of these AEs difficult. If the term 'immune mediated adverse reactions', or 'events', was used for all of these AEs, it would be more evident that these present across a spectrum of severity, and that they may, or may not, require immunosuppression. The overall frequency of occurrence would also be clearer. See Question 30: Terminology and immune mediated AEs, in Section 11, below.

Definitions

The following information regarding these terms is provided in the interim CSRs:

- Select AEs:

'In order to characterize AEs of special clinical interest that are potentially associated with the use of nivolumab, the Sponsor identified select AEs based on the following 4 guiding principles:

  - *AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies*
  - *AEs that may require immunosuppression (e.g. corticosteroids) as part of their management*
  - *AEs whose early recognition and management may mitigate severe toxicity*
  - *AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization'*

On the basis of the types of AEs previously observed across studies of nivolumab monotherapy, endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash were considered to be select AEs in Studies CA209205 and CA209039. Multiple event terms that could be used to describe each of these were grouped into endocrine, GI, hepatic, pulmonary, renal, and skin select AE categories, respectively. Analysis of select AES was limited to a reporting period of 30 days post nivolumab dose.

Hypersensitivity/infusion reactions were analysed together with the Select AE categories as multiple event terms could be used to describe such events, although these reactions were not considered to otherwise meet criteria of Select AEs.

Evaluation and management guidelines for the treatment of AEs, including Select AEs, were apparently provided to investigators in the Investigator Brochure for sites in all countries to assist in their identification and treatment.

- Immune mediated AEs (IMAEs)

In the CSRs, IMAEs were described as are specific events or categories that were of '*special clinical interest*'. They include the categories of demyelination event, diabetes mellitus, encephalitis, Guillain-Barre Syndrome, myasthenic syndrome, hypersensitivity, pancreatitis, uveitis, the specific endocrinopathies of adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, hypothyroidism/thyroiditis and thyroiditis together with the categories from the 'select AEs' of diarrhoea/colitis, hepatitis, nephritis and renal dysfunction, pneumonitis, rash. Multiple event terms were used in the search strategies for these AEs, with the terms used similar but not the same as the groupings used in 'select AEs'.

No definition of IMAEs was provided other than the PT terms used for each category/event. No rationale for the selection of these specific categories/events is provided although they comprise the AEs included under 'Select AEs' and '*Other Immune-related adverse reactions'* in the PI.

Analysis of IMAEs was for a reporting period of 100 days from last nivolumab dose and to patients who received immune-modulating medication for treatment of the event, with the exception of endocrine events (adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus). The rationale for the inclusion of endocrinopathies without the requirement for the use of immunosuppression use was '*that these events are often managed without immunosuppression'*.

Comment: This definition of IMAE requires that the investigator consider an immune mediated process as a possible cause of the patient's illness and also treats this illness with immunosuppression. From the narratives provided, there were a number of cases in which an immune mediated process was not considered and immunosuppression was not administered. This occurred despite investigator training and the provision of the Investigator's Brochure.

· Other Events of Special Interest

In the CA209205 CSR and the SCS, other events of special interest (OESI) were listed as demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, pancreatitis, and uveitis. These were further defined in the SCS by: '*Other events of special interest (OESIs) are events that do not fulfill all criteria to qualify as select AEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management, but do not benefit from pooling of multiple AE terms for full characterization and are therefore presented as unique events rather than using select AE methodology.'*

· Other IMAEs of special interest

This category is used in the CSR for Study CA209039 but not in the Study CA209205 CSR or the SCS. It has the same list of conditions as OESI but immunosuppressive therapy is required.

Comment: A patient with pancreatitis in CA209039 was not considered an IMAE of special interest due to not receiving immunosuppressive therapy. A patient with pancreatitis in CA209205 would be considered a OESI regardless of whether immunosuppressive therapy was required.

8.7.6.2. Search terms used for Select AEs and IMAEs

Comparison of the composite group of PTs used in each category (as provided in the appendices of the CSRs and SCS) suggests that the search strategy for IMAEs uses fewer broad terms and is largely a subset of select AEs.

Table 58. Composite PTs used for several sub-categories of AEs common to both 'select AEs' and IMAEs

Category	PTs used to identify 'select AEs' in this category	PTs used to identify 'IMAEs' in this category
Gastrointestinal	Autoimmune Colitis Colitis Colitis Ulcerative Diarrhoea Enteritis Enterocolitis Frequent Bowel Movements	Autoimmune Colitis Colitis Diarrhoea Enterocolitis

Category	PTs used to identify 'select AEs' in this category	PTs used to identify 'IMAEs' in this category
	Gastrointestinal Perforation	
Pulmonary	Acute respiratory distress syndrome Acute respiratory failure Interstitial lung disease Lung infiltration Pneumonitis	Interstitial lung disease Pneumonitis
Renal	Acute kidney injury Blood creatinine increased Blood urea increased Creatinine renal clearance decreased Hypercreatininaemia Nephritis Nephritis allergic Nephritis autoimmune Renal failure Renal tubular necrosis Tubulointerstitial nephritis Urine output decreased	Acute kidney injury Blood creatinine increased Nephritis Nephritis allergic Renal failure Tubulointerstitial nephritis
Hepatic	Acute hepatic failure Alanine aminotransferase increased Aspartate aminotransferase increased Autoimmune hepatitis Bilirubin conjugated increased Blood alkaline phosphatase increased Blood bilirubin increased Drug-induced liver injury Gamma-glutamyltransferase increased Hepatic enzyme increased Hepatic failure Hepatitis Hepatitis acute Hepatotoxicity Hyperbilirubinaemia Liver disorder Liver function test abnormal Liver injury Transaminases increased	Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Blood bilirubin increased Hepatitis Hepatitis acute Hepatotoxicity Hyperbilirubinaemia
Skin	Autoimmune Dermatitis Blister Dermatitis Dermatitis Exfoliative Drug Eruption Eczema Erythema	Autoimmune Dermatitis Rash Rash Maculo-Papular

Category	PTs used to identify 'select AEs' in this category	PTs used to identify 'IMAEs' in this category
	Erythema Multiforme Exfoliative Rash Palmar-Plantar Erythrodysaesthesia Syndrome Photosensitivity Reaction Pruritus Pruritus Allergic Pruritus Generalised Psoriasis Rash Rash Erythematous Rash Generalised Rash Macular Rash Maculo-Papular Rash Papular Rash Pruritic Skin Exfoliation Skin Hypopigmentation Skin Irritation Stevens-Johnson Syndrome Toxic Epidermal Necrolysis Urticaria Vitiligo	
Note: not all categories of select AEs and IMAEs have been included in this table.		

From the descriptions provided in the sponsor's documents, the choice of 'select AEs' and 'IMAEs', and their definition using 'composite groups' of preferred terms and duration of reporting period, appears to be arbitrary. Separation into 'select AEs' and 'IMAEs' also appears to be arbitrary as they are all potentially immune mediated adverse reactions. The use of less broad search terms for IMAE categories could potentially result in 'select AEs' that are treated with immunosuppression but are not classified as IMAE.

'*Other events of special interest (OESIs)*' appear to be an arbitrarily selected group of rarer AEs that may have an immune basis and that have occurred in other nivolumab studies. These events are also defined by the PTs used in the search given in SCS appendix. Table 59 below shows the terms used for demyelination, encephalitis and Guillain-Barre syndrome.

Table 59. Examples of composite PTs used for IMAEs, including OESI

Protocol: Summary of Clinical Safety

Immune-Mediated Adverse Event Definition

Category	Preferred Terms
ADRENAL INSUFFICIENCY	ADRENAL INSUFFICIENCY
DEMYELINATION EVENT	AUTOIMMUNE DEMYELINATING DISEASE DEMYELINATION
DIABETES MELLITUS	DIABETES MELLITUS DIABETIC KETOACIDOSIS FULMINANT TYPE 1 DIABETES MELLITUS TYPE 1 DIABETES MELLITUS
DIARRHEA/COLITIS	AUTOIMMUNE COLITIS COLITIS DIARRHOEA ENTEROCOLITIS
ENCEPHALITIS EVENT	ENCEPHALITIS ENCEPHALITIS ALLERGIC ENCEPHALITIS AUTOIMMUNE ENCEPHALITIS BRAIN STEM ENCEPHALITIS HAEMORRHAGIC ENCEPHALITIS LETHARGICA ENCEPHALITIS TOXIC LUPUS ENCEPHALITIS NONINFECTIVE ENCEPHALITIS PANENCEPHALITIS RASMUSSEN ENCEPHALITIS SUBACUTE SCLEROSING PANENCEPHALITIS
GUILLAIN-BARRE SYNDROME	GUILLAIN-BARRE SYNDROME MILLER FISHER SYNDROME
HEPATITIS	ALANINE AMINOTRANSFERASE INCREASED ASPARTATE AMINOTRANSFERASE INCREASED AUTOIMMUNE HEPATITIS BLOOD ALKALINE PHOSPHATASE INCREASED BLOOD BILIRUBIN INCREASED

MedDRA Version: 18.0
Program Source: /projects/bms211280/stats/SCS/prog/tables/rl-ae-imaedef.sas

8.7.6.3. Occurrence of immune mediated AEs (select AEs versus IMAEs)

Using tables from the interim CSRs, the evaluator has compiled a table of AEs by PT compared to reported Select AEs and IMAEs (all grade) using the extended reporting period of 100 days for Study CA209039 and Study CA209205 (see Table 60, below). This presentation is limited as results were not shown for all categories in each group. However, the table does show that of the AEs identified as possibly due to immune mediated mechanisms (using multiple PT search strategies), the most frequently reported were colitis/diarrhoea, hypothyroidism and rash; the rate of reports for these common immune mediated AEs were lower in Cohorts A and C compared to Cohort B; numerically IMAEs are a subset of select AEs for these categories (when a reporting period of 100 days is used); reports in other categories were rare; and very few of these AEs were treated with immunosuppressive therapy (on the basis that IMAE are partly defined by treatment with immunosuppression (except for endocrinopathies)).

Table 60. Study CA209039 and CA 209205: Select AEs[1] and IMAEs[2] (extended follow-up period of 100 days)

AE category	**Study CA209039** (n = 23)			**Study CA209205 Cohort B** (n = 80)			**Study CA209205 Cohort A + C** (n = 160)		
	All cause, any grade[3]	Select AE	IMAE	All cause, any grade[3]	Select AE[4]	IMAE	All cause, any grade[3]	Select AE	IMAE
Endocrinopathies									

AE category	Study CA209039 (n = 23)			Study CA209205 Cohort B (n = 80)			Study CA209205 Cohort A + C (n = 160)		
	All cause, any grade[3]	Select AE	IMAE	All cause, any grade[3]	Select AE[4]	IMAE	All cause, any grade[3]	Select AE	IMAE
adrenal insufficiency			0		1	1		0	0
diabetes mellitus			0		0	0		1	1
hyperglycaemia	5			8			6		
hyperthyroidism			1		1	1		1	1
hypothyroidism (primary; or thyroiditis)			4	7	12 (15%)	11	7	9 (5.6%)	10
GI event									
colitis/diarrhoea	12	12 (52%)	0	22	22 (27.5%)	0	29	30 (18.8%)	1
Hepatic event		9							
autoimmune hepatitis, hepatitis			0		1	0		1	1
hepatotoxicity								1	
abnormal LFTs		1			1			1	
increased transaminases								2	
increased ALT	5	5		4	4	2		8	
increased AST	4	4		5	5	2		2	
increased ALP	3	3		4	4	1	8	8	
increased bilirubin	1	1			1			1	
increased GGT								1	
Respiratory event									
Acute respiratory distress syndrome								1	
Pneumonitis	3	3	2		2	2		5	2
bronchospasm		2			2	0		1	
Renal event									
Increased creatinine	2			4	4	0		3	
autoimmune nephritis								1	
acute kidney injury		2							
Skin event									
dermatitis					1	0		0	
erythema					1	0			
photosensitivity reaction								1	
pruritus	9	9			12	0		15	
psoriasis					1	0			

AE category	Study CA209039 (n = 23)			Study CA209205 Cohort B (n = 80)			Study CA209205 Cohort A + C (n = 160)		
	All cause, any grade[3]	Select AE	IMAE	All cause, any grade[3]	Select AE[4]	IMAE	All cause, any grade[3]	Select AE	IMAE
rash: macular, maculo-papular, papular, pruritic	13	14 (61%)	3	17	21 (26.3%)	9	12	16 (10%)	2
skin exfoliation	1	9						1	
urticaria					1	0		1	
Other									
hypersensitivity		1	1		1	0		4	1
infusion related reaction	1	1		16	16 (10%)	5	15	15 (9.4%)	2

1) 'select AEs': defined by search strategy using multiple PTs for pre-determined categories; may or may not require treatment with immunosuppression; reporting period usually 30 days; 2) IMAEs': defined by search strategy using multiple PTs for pre-determined categories; require treatment with immunosuppression (except for endocrinopathies); reporting period of 100 days; 3) AEs by single PT; 4) Select AEs (extended-follow up).

Due to the small numbers of cHL patients treated with nivolumab, the rarity of some of these AEs, and due to the varying exposure to nivolumab in the cHL population, determining rates that are generalisable to the intended target population is difficult. The rates reported for the integrated cHL population for the more common AEs may under-estimate the true rate; rarer events are unlikely to have occurred in the small populations of Study CA209039 and Cohort B. Determining the full course of the AEs is also difficult, given the limited follow-up of the Cohort A and Cohort C patients at the time of the interim analysis of Study CA209205.

8.7.6.4. Attribution of drug related or not

Many of the AEs described as select AEs or IMAEs or OESIs have non-specific presentations. As a result, the assessment of these AEs as possibly being drug related is dependent on the investigators understanding and recognition of this new class of adverse effects. This recognition varied in the two studies presented in the dossier:

- Among subjects treated with nivolumab in all cohorts of Study CA209205 (263 patients), there were 215 select AEs reported. The interim CSR states that '*The majority of select AEs reported were Grade 1 or 2, and most were considered drug-related by the investigator*.'
- From a table in the CSR for Study CA209039, there were 52 reports of select AEs among the 23 cHL subjects treated with nivolumab. The interim CSR states that '*The majority of Select AEs reported was Grade 1-2 and were considered not drug-related by the investigator*'.

Comparison of rates of categories of select AEs considered drug-related versus not drug related in the two studies confirms these statements (see descriptions below).

Comment: The sponsor is asked to comment on why most select AEs were considered drug related by the investigators of Study CA209205 but were not considered drug related by the investigators of Study CA209039, including a description of the training provided to the investigators in each study regarding the recognition and management of AEs that are potentially immune-mediated. See Question 32: Select AEs drug related or not; the investigators of Study CA209205 and Study 209039 in Section 11, below.

8.7.6.5. Summary of events

Study CA209205 Select AEs

From a table of the CSR, there were 98 reports of select AEs in Cohort B patients, 56 reports in Cohort A and 61 reports in Cohort C. Of these reports, none were Grade 5. There were 7 patients with Grade 3 or 4 events reported in Cohort B, 3 patients in Cohort A and 8 in Cohort C.

Table 61. Study CA209205 Select AEs, all causality

Category	Cohort B **n = 80**	Cohort A **n = 63**	Cohort C **n = 97**
Endocrine	14 (17.5)	9 (14.3)	5 (5.2)
Gastrointestinal	21 (26.3)	17 (27)	12 (12.4)
Hepatic	8 (10)	3 (4.8)	11 (11.3)
Pulmonary	1 (1.3)	1 (1.6)	5 (5.2)
Renal	4 (5.0)	2 (3.2)	2 (2.1)
Skin	33 (41.3)	16 (25.4)	14 (14.4)
Hypersensitivity/Infusion Reaction	17 (21.3)	8 (12.7)	12 (12.4)
Total select AEs	98	56	61

Grade 3 to 4 events:

- Cohort B
  - Hepatic category: 4 patients with 6 reports including blood alkaline phosphatase increased (n = 1), ALT increased (n = 2), AST increased (n = 2) and autoimmune hepatitis (n = 1)
  - Skin category: 3 patients with 3 reports including rash (n = 2) and rash maculopapular (n = 1)
- Cohort A
  - Gastrointestinal category: one patient with one report of diarrhoea
  - Hepatic category: one patient with two reports, one each of ALT increased and hepatitis
  - Hypersensitivity/infusion reaction category: one patient with one report of hypersensitivity
- Cohort C
  - Hepatic category: 4 patients with 6 reports, including blood alkaline phosphatase increased (n = 3), one each of ALT increased, GGT increased and hepatitis
  - Pulmonary category: one patient with one report of acute respiratory distress syndrome
  - Hypersensitivity/infusion reaction category: one patient with one report of hypersensitivity
  - Renal category: one patient with one report of nephritis autoimmune
  - Skin category: 1 patient with one report of rash.

Study CA209205 IMAEs

There was a total of 25 endocrine IMAEs with 14 events in Cohort B, 7 in Cohort A and 5 in Cohort C.

Of the non-endocrine events that were treated with corticosteroids and that occurred within 100 days of the last dose, there were:

- 6 events of hepatitis
- One event of diarrhoea/colitis
- 4 events of pneumonitis
- 11 events of rash
- 8 hypersensitivity events
- Rash: 3 subjects (one maculopapular), all Grade 1 or 2
- Hypersensitivity/infusion related reaction, 1 patient, Grade 2.

Study CA209039 Select AEs

Among all cHL subjects treated with nivolumab, there were 52 reports of select AEs. Of these, there were no Grade 5 events and 4 Grade 3 or 4 events. All other select AEs were Grade 1 or 2.

Table 62. Study CA209039 Select AEs

Category	Number (%)	Grade 3 or 4 events	Grade 3 or 4 event comment
Endocrine	5 (21.7)	0	
Gastrointestinal	11 (47.8)	2	one event each for diarrhoea and colitis
Hepatic	9 (39.1)	1	one event of 'liver function test abnormal'
Pulmonary	2 (13)	1	one event of pneumonitis
Skin	14 (60.9)	0	
Hypersensitivity/Infusion Reaction	4 (17.4)	0	

Study CA209039 IMAEs

AEs categorised as IMAEs were:

- Hypothyroidism: 4 patients, all events Grade 2
- Hyperthyroidism: One patient, Grade 2
- Pneumonitis: 2 patients, one Grade 2 and one Grade 3 with one of these patients treated with corticosteroids
- There were no other IMAEs except for one patient who discontinued nivolumab treatment due to a drug-related SAE of Grade 3 pancreatitis *'who required no immune-modulating medication and therefore not classified as an IMAE.'*

Comment: The criterion of treatment with immune-modulating medication does not appear to be consistently applied given that one patient with the IMAE of pneumonitis did not receive immune-modulating medications.

8.7.6.6. Descriptions of possible immune mediated adverse reactions

Comment: The descriptions provided in the SCS were limited to select AEs within the reporting period of 30 days and that were considered drug-related by the investigators, together with Other Events of Special Interest. Given the different approaches taken

by the investigators in the two studies, with the Study CA209205 investigators considering most select AEs to be drug related and the investigators in Study CA209039 considering most select AEs to not be drug related, then most of the select AEs from the latter study are not included in the descriptions provided. IMAEs were also not described. As a result any events that occurred between 30 and 100 days of the last dose of nivolumab were not included in the sponsor's description, except for OESI. The summaries according to categories in the CSRs were also limited to those patients in whom the event was considered drug related.

The evaluator has based the following descriptions on the information provided in the interim CSRs, combining the information for 'select AEs' and IMAEs and using a reporting period of 100 days where possible. The SCS has been referred to for summaries of the AEs in each category, noting that this only includes patients in whom the event was reported within 30 days of last dose and in whom the event was considered drug related. To address the above concerns, the sponsor is asked to provide a revised presentation of select AEs with this including updated data (see Question 31: Descriptions of select AEs and OESIs, in Section 11, below).

Summaries of individual patient narratives have been provided for many of the patients requiring immunosuppressive therapy to provide a better picture of the patient's experience. These summaries and other narratives describe patients with complex illnesses and in whom many events that could be immune mediated were reported. Recognition of these events as potentially immune mediated, with appropriate assessment and consideration of treatment with corticosteroids, was extremely variable. This is best shown in some of the patients with respiratory complications, with this commonly described as broncho-pneumonia or respiratory tract infection (even when a CT scan is reported as 'pneumonitis' or 'alveolitis') or 'acute respiratory distress syndrome', with corticosteroids only commenced after the patient has failed to improve on broad spectrum antibiotics. There were also cases of pleural effusions, pericardial effusion, meningitis/encephalitis, general deterioration and other non-specific illnesses in which immune-mediated causes of SAEs did not appear to have been considered. This resulted in delayed (or no) administration of immunosuppressive therapy and may have resulted in worse patient outcomes. Courses of corticosteroids were also variable, with this therapy ceased immediately on resolution of the event in some cases, with subsequent recurrence of the event. The evaluator notes that this apparent failure to consider immune-mediated causes for serious events with non-specific presentations and seemingly haphazard administration of corticosteroids occurred despite an investigator's brochure that described such events and their appropriate treatment. This raises concerns regarding how well immune-mediated complications may be recognised and treated outside the clinical trial setting.

1.1.1.2.1. Endocrine events

Endocrine events include PTs of adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus. The reporting period for the description of these events is 100 days.

Adrenal insufficiency

Adrenal insufficiency reported in one patient (Study CA209205). The event was of Grade 2 severity not requiring dose delay or discontinuation. It occurred after 6 weeks of treatment and resolved over 13 weeks. Low dose hydrocortisone (20 mg daily) was administered during this time. Treatment with nivolumab was resumed without recurrence.

Hypophysitis

There were no reports of hypophysitis.

Diabetes mellitus

Grade 1 diabetes mellitus was reported in one patient (Study CA209205) on the basis of elevated blood glucose measurements. No action was taken and nivolumab therapy continued.

Hypothyroidism/thyroiditis, hyperthyroidism

Thyroid function abnormalities were mainly detected through regular laboratory testing of thyroid function.

Study CA209039: Hypothyroidism was reported in 4 patients, all Grade 1 or 2.

Study CA209205: Hypothyroidism was reported in 24 patients, hyperthyroidism in 3 and thyroiditis in 2. All events were Grade 1 or 2. The time to onset ranged from the first dose to 26 weeks and 12 patients were treated with levothyroxine. No patients were treated with immunosuppressive therapy. In the Cohort B patients, the event resolved in 5/11 patients; the median time to resolution was 20 weeks. One patient was re-challenged without recurrence.

Comment: Note that many patients required ongoing levothyroxine, with 'resolution' being normalisation of the TFT abnormalities.

Hyperthyroidism

Hyperthyroidism was reported in 2 patients in Study CA209205 and 1 patient in Study CA209039.

Both patients in Study CA209205 were treated with methimazole; one also was treated with corticosteroids (see description below). Both were rechallenged and one had no recurrence.

One patient on thyroxine replacement therapy for prior hypothyroidism developed clinically symptomatic hyperthyroidism after the third dose of nivolumab. Thyroxine replacement was ceased and the patient commenced on methimazole. Nivolumab therapy was with-held. The patient was subsequently also commenced on corticosteroid (prednisolone 40mg alt days) and methimazole ceased. The corticosteroid dose was tapered over 100 days and nivolumab therapy recommenced with no apparent recurrence of hyperthyroidism.

8.7.6.7. Gastrointestinal events

For the 100 day reporting period, diarrhoea/colitis occurred in 52 patients in Study CA209205 and 11 patients in Study CA209039. The event was considered drug related in 27/52 patients in Study CA209205 and 4/11 in Study CA209039.

SCS

Of the 29 patients in whom the event was reported within 30 days of last dose and was considered drug-related:

- All subjects reported diarrhoea and 1 subject also reported colitis
- The majority of events were Grade 1 or 2; there was 1 Grade 3 event (diarrhoea) reported. There were no Grade 4 or 5 events reported
- 1 event (Grade 3 diarrhoea) was considered an SAE. No events led to discontinuation of study therapy
- The time to onset ranged from first dose to 15 weeks (median 3.43 weeks)
- 1 subject was treated with immune-modulating medication (high-dose corticosteroids), a summary of the narrative for this patient is provided below
- 26/29 (92.9%) subjects had resolution of their events with time to resolution ranging from 1 day to more than 25 weeks (ongoing at DBL).

Narrative summary

One patient was hospitalised with Grade 2 diarrhoea after the second dose of nivolumab that resolved with non-specific treatment. The third dose was administered with Grade 3 diarrhoea recurring several days later. This initially improved and then worsened, requiring hospitalisation. The next dose of nivolumab was delayed and corticosteroid treatment commenced. This was tapered over 30 days and then ceased. Several days later the patient was again hospitalised with Grade 3 diarrhoea. Non-specific treatment was provided with the event of diarrhoea resolving over 2 weeks. No further nivolumab was administered but this was not formally discontinued until 80 days later when the patient was found to have progressive disease. At the time of DBL, another 100 days later, the event of diarrhoea was described as ongoing.

8.7.6.8. Hepatic events

Hepatic events were reported in 9 patients in Study CA209039 and 22 patients in Study CA209205. Of these, the events were considered drug related in 2/9 patients and 14/22 patients respectively.

SCS

Of the 16 patients in whom the event was reported within 30 days of last dose and was considered drug-related:

- ALT increased, AST increased, and blood ALP increased were the most frequently reported terms (> 2.0% of subjects)
- The majority of events were Grade 1 or 2. Grade 3 or 4 events were reported in 6 subjects. GGT increased was the only Grade 4 event and was reported in 1 subject. There were no Grade 5 events reported. One 1 event (Grade 3 ALT increased) was also reported as an SAE
- 3 subjects had events that led to discontinuation of study therapy (ALT and AST increased in 1 subject, autoimmune hepatitis in 1 subject, and hepatitis in 1 subject; all Grade 3)
- The time to onset ranged from one to 38 weeks (median 6.43 weeks)
- 6 patients were treated with high dose corticosteroid therapy for a range of 3 to 36 weeks
- 7 (43.8%) subjects had resolution of their events, including 4 of the patients treated with corticosteroids
- The time to resolution ranged from 2 to more than 24 weeks, with some patients having ongoing symptoms at the time of DBL.

Narrative summaries

- One patient was reported to have autoimmune hepatitis developing 14 days after dose 7 of nivolumab. The patient was commenced on high dose corticosteroids (prednisolone 160 mg alternate days) with this tapered over the next 60 days. Study drug was with-held during this time and not recommenced due to disease progression, the episode of hepatitis and the subsequent development of osteomyelitis.
- One patient developed Grade 3 increased ALT after the third dose of nivolumab. The next dose was delayed and the patient was treated with high dose corticosteroids, tapering to prednisolone 10 mg daily over the next 2 weeks as the event resolved. The fourth dose of nivolumab was then administered. Grade 3 hepatitis was reported 13 days after this dose, with nivolumab treatment then discontinued due to this event. High dose corticosteroids were recommenced and then tapered over the next 30 days, with resolution of the event reported.
- One patient was reported to develop Grade 2 hepatotoxicity on the basis of increased ALT, AST and total bilirubin on the day of the dose 6 of nivolumab. This was considered drug related and high dose corticosteroid therapy was commenced (oral prednisolone 40 mg

daily, tapered over 40 days). Doses 6 to 9 of nivolumab were administered without delay. The hepatotoxicity was reported to have resolved during the steroid taper. Nivolumab treatment was discontinued after dose 9 due to disease progression.

- One patient developed Grade 3 increase in ALT 14 days after dose 4 of nivolumab. This was considered drug-related and the patient was treated with high dose corticosteroids (methylprednisolone 80 mg BD), broad spectrum antibiotic and the next dose of nivolumab was delayed. Corticosteroids were ceased after 2 days as the increased ALT was reported to have resolved. Two days later the patient was hospitalised with Grade 3 increase in ALT and methylprednisolone was recommenced at higher dose (120 mg TDS). Six days later, treatment with mycophenolic acid (an immunosuppressant) was added. The event of increased ALT was reported to resolve 5 days later and mycophenolic acid was ceased after a treatment course of 7 days. Corticosteroid treatment with intravenous methylprednisolone was followed by an oral taper over 50 days. Treatment with nivolumab was resumed during the steroid taper without reported recurrence of the event.

8.7.6.9. Pulmonary events

There were 3 reports of pulmonary events in Study CA209039, with the event of pneumonitis considered to be drug related. There were 8 reports of pulmonary evens in Study CA209205. Of these 7 were pneumonitis and one was acute respiratory distress syndrome; 5 of the episodes of pneumonitis were considered to be drug related. The report of Grade 3 acute respiratory distress syndrome was not considered drug related (see summary of narrative below).

SCS

Of the 6 patients in whom the event was reported within 30 days of last dose and was considered drug-related:

- All events were assessed as Grade 1 or 2, although 3 were considered SAEs and in one case resulted in treatment discontinuation
- The time to onset ranged from the first dose to 17 weeks
- Three patients were treated with immunosuppressive therapy (see summaries of narratives below)
- Three patients had resolution of the event over a 1 to 7 weeks period.

Narrative summaries

- One patient developed abnormal LFTs after dose 3 of nivolumab, with the subsequent dose delayed. In the interim, the patient was hospitalised with Grade 3 dyspnoea. This was treated with high dose corticosteroid therapy with this tapered over the next 2 weeks. A subsequent CT scan at the end of this taper was consistent with pneumonitis and treated with broad spectrum antimicrobial drugs and an increase in corticosteroid dose. The dyspnoea resolved over the next week and the patient was discontinued from nivolumab treatment. One week later, during corticosteroid taper, the patient was hospitalised with Grade 3 pneumonitis and treated with increased corticosteroids and anti-fungal therapy. Corticosteroid therapy was again tapered but needed to be increased again. Around this time the patient was lost to follow up and died some 200 days later. The patient was reported to still be receiving corticosteroid therapy at the time of death.
- One patient was hospitalised with Grade 2 pneumonitis after dose 4 of nivolumab. The patient was symptomatic with desaturation, tachycardia and cough; CT chest was said to be consistent with pneumonitis (not described). The event was considered drug related and the patient was commenced on high dose corticosteroids (methylprednisolone 80 mg BD followed by prednisolone at 100 mg BD) and broad spectrum antibiotic. The next dose of nivolumab was delayed. Steroids were administered for a total of 5 days and ceased due to 'resolution of pneumonitis'. Nivolumab therapy had been administered a further 8 times to DBL, without recurrence.

- One patient developed a rash requiring corticosteroid treatment after the fourth dose of nivolumab. After dose 8, the patient developed pneumonia with infiltrate on CT chest. This was treated with antibiotics. Repeat scan 15 days later, at the time of the dose 9, was consistent with pneumonitis. Several days later, the patient was diagnosed with pneumonitis on the basis of cough and dyspnoea and a prolonged course of corticosteroids was administered. Nivolumab treatment was continued. The pneumonitis subsequently resolved. The patient's course was subsequently complicated by hypothyroidism and arrhythmia (no details regarding the nature of the arrhythmia were provided).
- One patient developed a Grade 2 infusion related reaction (not described) with the first dose of nivolumab that was treated with intravenous dexamethasone without interruption of the infusion. This patient was also reported to have a respiratory infection at the time that was treated with antibiotics. A drug related Grade 2 'lung infection' was also reported at the time of the second dose. This was treated with antibiotics. Fourteen days later the patient was commenced on oral prednisolone 30 mg daily for the 'lung infection'. This was tapered over two weeks. Two further doses of nivolumab were given without recurrence of the respiratory condition. Treatment was then ceased due to disease progression.
- One patient had several episodes of 'bronchopneumonia' after 7 doses of nivolumab. Treatment was continued and CT chest 2 doses later showed alveolitis. Corticosteroids were administered for one day and the outcome for this event was not reported. Nivolumab treatment was continued. The patient subsequently received courses of corticosteroids for neuritis and for myalgia (no CK reported). Hypothyroidism also developed, this was treated with levothyroxine. At the time of DBL, the events of fatigue and myalgia were ongoing, as was treatment with levothyroxine.
- One patient developed *Pneumocystis jiroveci* pneumonia after the third dose of nivolumab. This resolved with anti-microbial therapy and corticosteroids. Nivolumab treatment was resumed after steroid taper was completed (Day 67). The patient was noted to have Grade 1 hypothyroidism on routine laboratory testing. On the day of planned Day 124 nivolumab dose, the PET/CT scan showed immune mediated pneumonitis and atypical pneumonia, described as Grade 2 pneumonitis by the Investigator. Nivolumab was with-held and no subsequent doses administered. A bronchoscopy 'showed coronaviriidae' and the episode of pneumonitis received no specific treatment. Around 10 days later, the patient was hospitalised with respiratory distress, assessed as Grade 3 pneumonitis and treated with corticosteroids.

The following is summarised from the narrative of the patient with acute respiratory distress syndrome. From the information provided in the narrative, an immune mediated cause cannot be excluded.

- One patient developed rapidly progressive respiratory failure on the day after the first dose of nivolumab. This was reported as acute respiratory distress syndrome and not related to nivolumab. It was treated with corticosteroids and CPAP. The patient improved over the next week and steroids were ceased. The patient was re-admitted to hospital 20 days later with respiratory insufficiency that was described as being due to 'lung progressive disease' with no further details. No further nivolumab doses had been administered at the time of DBL (Day 27).

8.7.6.10. Renal events

There was one renal event (one Grade 1 or 2 and one Grade 4 acute kidney injury) reported in Study CA209039. Neither was considered drug related. There were 8 renal events reported in Study CA209205 (7 increased creatinine, all Grade 1 or 2, and one Grade 3 autoimmune nephritis). Of these, 4 events were considered drug related.

SCS

Of the 4 patients in whom the event was reported within 30 days of last dose and was considered drug-related:

- There were no Grade 5 events. No events were considered SAEs
- The event of autoimmune nephritis resulted in discontinuation of nivolumab
- The time to onset ranged for 1 to 24 weeks (median 7 weeks)
- One patient was treated with high dose corticosteroids for a duration of 3 weeks
- The event resolved in 2 patients, with this not including the patient treated with corticosteroids
- The time to resolution ranged from 1 to more than 24 weeks with the event ongoing in some patients at DBL.

8.7.6.11. Skin events

Skin events were reported in 14 patients in Study CA209039, with this considered drug related in 5 patients. Skin events were reported in 63 patients in Study CA209205 with this considered drug related in 43 patients.

All causality skin events reported in both studies for the 100 day reporting period were: pruritus (n = 44), rash (n = 39), rash maculopapular (n = 7), other types of rash (n = 13), skin exfoliation/dermatitis exfoliative (n = 2). All events were Grade 1or 2 except for 3 Grade 3 or 4 events of rash and one Grade 3 or 4 event of pruritic rash.

SCS

Of the 48 patients in whom the event was reported within 30 days of last dose and was considered drug-related:

- The majority of events were Grade 1 or 2. Grade 3 events were reported in 3 subjects (rash in 2 subjects, rash maculo-papular in 1 subject). No Grade 4 or 5 events were reported.
- 1 event of Grade 3 rash was considered an SAE. No events led to discontinuation of study therapy
- The time to onset ranged from first dose to 61 weeks (median 7 weeks)
- 15 subjects were treated with immunosuppressive medication, including 1 subject who received high-dose corticosteroids (see narrative summary below).
- 31 (66.0%) subjects had resolution of their events, including 11 of the patients who received immunosuppressive medications.
- The time to resolution for any grade event ranged from 1 to 40 weeks (median 8 weeks).

Narrative summaries

- One patient was hospitalised with a rash (no description provided) 18 days after the first dose of nivolumab. The patient was commenced on high dose steroids with the rash ongoing and no further nivolumab administered at the time of DBL
- One patient had recurrent episodes of pyrexia during nivolumab treatment. The first occurred after dose 7 and was treated with broad spectrum antimicrobial drugs. The second episode occurred after dose 11 and was associated with a rash (not described) and decreased platelet count. This was initially attributed to Varicella Zoster and then to ITP, with prednisolone commenced at 20 mg daily. None of these events were considered drug-related, the patient was discontinued from nivolumab treatment at the time of the second episode due to disease progression, although CT chest/abdomen/pelvis was reported as 'normal' and disease at Baseline was hilar and right lung.

8.7.6.12. Other events of special interest

Other events of special interest for the nivolumab program include: myasthenic syndrome, demyelination, Guillain-Barré syndrome, pancreatitis, uveitis, and encephalitis. No events of myasthenic syndrome, demyelination, or Guillain-Barré syndrome were reported in the studies.

In the Integrated cHL Population (including both Studies CA209039 and CA209205), there were 6 subjects that had OESIs within 100 days of last dose of nivolumab (2 with pancreatitis, 3 with a uveitis event (2 uveitis, 1 iritis), and 1 with encephalitis).

Pancreatitis

There were two patients with pancreatitis, one in Study CA209039 and one in Study CA209205. In one patient, it resulted in discontinuation of treatment. In neither patient was immunomodulatory medications administered.

Uveitis

There were 2 patients with uveitis and one patient with iritis reported. These were all Grade 2 events. In 2 of the 3 cases, the patient was treated with topical corticosteroids. In one case the patient received both topical and systemic corticosteroids (see narrative summary below).

Narrative summary

One patient was reported to develop a Grade 2 infusion reaction 11 days after the second dose of nivolumab (no description provided). Two days later the patient was reported to develop Grade 1 uveitis of the right eye that was not considered drug related. Nivolumab treatment was continued and no action taken. Ten days after the fourth dose of nivolumab, the patient was reported to have Grade 2 uveitis and retinitis. Treatment with corticosteroid eye drops and oral prednisolone was commenced, together with anti-inflammatory drugs (ketorolac, meloxicam), antibiotics (clindamycin, gentamicin) and metimazole (sic). Treatment with oral prednisolone was continued for 2 weeks and the eyedrops for 26 days. At this time repeat eye examination showed 'retinitis macular affection'. The event of uveitis was reported to be ongoing at DBL 2 weeks later.

Encephalitis

There was one event of encephalitis (see summary below).

Narrative summary: This patient continued nivolumab treatment after initial disease progression and achieved PR. After a last dose of nivolumab on Day 106, the patient discontinued for the study to undergo an allo-SCT on Day 116. Shortly after the allo-SCT, the patient was hospitalised with febrile neutropaenia. On Day 148, the patient was hospitalised with GVHD and was commenced on immune-suppressive doses of corticosteroids (methylprednisolone and prednisolone. The patient was discharged on sirolimus and budesomide for GVHD; this was subsequently changed to mycophenolic acid. On Day 158, the patient was hospitalised with encephalitis that responded to foscarnet. On Day 187, the patient was hospitalised with MSSA bacteraemia, cryptosporidium infection and thrombotic microangiopathy. The patient progressively deteriorated with respiratory and renal failure and died on Day 223. The patient's death was attributed to complications of the allo-SCT.

Other OESI

OESI in the study protocols for the cHL studies were limited to the events that had been recognised as associated with nivolumab at that time. Other events have since been recognised and were discussed in the SCS.

SIRS

According to the SCS, following a report of a case of systemic inflammatory response syndrome (SIRS) requiring treatment with corticosteroids in RCC Study CA209025 (in which patients with

advanced RCC were treated with nivolumab monotherapy), SIRS was added to the product information. According to the SCS, there were no reports of SIRS in the cHL studies.

Comment: The evaluator notes that there was a report of multiple organ system failure in Study CA209205. MOSF is regarded as a more severe manifestation of SIRS . The narrative of this patient is provided above (see Section 8.7.3.1. Deaths in Study CA209205, above).

Toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN) was identified as an event of special interest based on 3 cases with fatal outcome identified in ongoing studies in the nivolumab program (1 case occurred on nivolumab monotherapy; 1 case occurred on subsequent Bactrim after discontinuation from nivolumab and ipilimumab (1 dose) due to ulcerative colitis; 1 case occurred on subsequent ipilimumab after discontinuation from nivolumab due to erythema multiforme).

According to the SCS, no events of TEN have been reported in the cHL population treated with nivolumab.

8.7.6.13. Hypersensitivity events/Infusion related reactions

Hypersensitivity/infusion reactions included the following terms: anaphylactic reaction, anaphylactic shock, bronchospasm, hypersensitivity, and infusion related reaction.

In Study CA209039, there were 4/23 (17.4%) patients in whom hypersensitivity/infusion reactions were reported. These included 2 reports of bronchospasm, one report of infusion related reaction (all Grade 1) and one patient in whom a Grade 2 immune mediated hypersensitivity category (infusion related reaction) was reported.

In Study CA209205, hypersensitivity category AEs occurred in 36 (15.0%) subjects and events that required immune-modulating medication were reported in 8 (3.3%) subjects.

SCS

Of the 37 patients in whom the event was reported within 30 days of last dose and was considered drug-related:

- The most frequently reported events were infusion-related reactions (32 of 37 subjects). Of these:
  - all were Grade 1 or 2, except for one Grade 3 event
  - The majority of subjects (75.0%, 24/32) only experienced one infusion-related reaction
  - 5 events (all infusion related reactions) were considered SAEs. No events led to discontinuation of study therapy
  - Infusion-related reactions developed early (90.6%, 29/32 subjects with onset of first event on the day of the first infusion (Day 1 of Cycle 1)
  - 8 subjects received corticosteroids for treatment, and infusion-related reactions resolved in all subjects within 48 hours.
- There was one Grade 3 hypersensitivity event. No Grade 4 or 5 events were reported.

The SCS noted that there was for a higher rate of infusion related reactions in the cHL group compared to other tumour types (see also Table 49 above for a summary of nivolumab safety across tumour types). The following explanation for this was provided by the sponsor: '*This may be attributed in part to a high incidence of infusion-related reactions that occurred at one CA209205 study center in Germany (15/30 treated subjects at the site had infusion related reactions), which accounted for 46.9% (15/32) of all infusion-related reactions in CA209205. Consequently, the observed incidence of infusion reactions in CA209205 was higher in Europe (18.3%) than in US/Canada (7.0%)'.*

Comment: No further information (in particular whether these patients with infusion related reactions were in Cohort B or the definition of infusion related reactions used in CA209205) could be located by the evaluator in the SCS or interim study report (see Question 35: Defining infusion related reactions in Section 11, below).

The incidence rate of hypersensitivity/infusion related reactions was similar in both Study CA209039 and CA209205 (17.4% and 15% respectively). The Summary of Clinical Pharmacology presentation of provides a summary of select adverse events in the hypersensitivity/infusion reaction category by ADA Status (positive or negative) for all subjects who were treated with nivolumab monotherapy and in whom the ICDIM 140 ADA assay was used (Studies CA209063, CA209037, CA209066, CA209017, CA209057, CA209067, CA209025, CA209039 and CA209205). This showed an incidence of hypersensitivity/infusion reaction category events of 9.6% for the total pooled population (see Table 17, above). This is considerably lower than the rates reported in both Studies CA209039 and CA209205. The sponsor is asked to provide a comparison of the incidence rates hypersensitivity/infusion reaction category events for patients with other tumour types (melanoma, NSCLC, RCC) treated with nivolumab monotherapy and to provide comment if this shows a difference across tumour types. See Question 34: Hypersensitivity/infusion related reaction category adverse events in cHL patients compared to other tumour types in Section 11, below.

Narratives were provided for the infusion related reactions as these were reported as 'other significant medical events'. These include the following patients:

- One patient developed a Grade 3 hypersensitivity reaction during the 10th dose of nivolumab. No further details were provided. The reaction resulted in delay of next dose and in prednisolone 40 mg administered on the day of the next dose and then daily for 14 days. The hypersensitivity event was then reported as resolved and did not recur with subsequent doses.
- One patient developed an infusion related reaction with first dose. This was treated with hydrocortisone 100 mg and the nivolumab dose completed. No recurrence was reported with subsequent doses (diphenhydramine administered with these doses).
- One patient developed a Grade 1 infusion reaction with the second dose of nivolumab, requiring no specific action, and a Grade 2 reaction with the fourth dose that was managed by dose interruption and administration of intravenous corticosteroids. The patient has received a further 20 doses without further infusion related reactions. The patient appears to have been treated with an immunosuppressive dose of prednisolone 25 mg for several months after the fourth dose of nivolumab. It is unclear from the narrative as to whether prednisolone was administered daily or as premedication for subsequent nivolumab doses.
- One patient developed a Grade 2 infusion related reaction with the first dose of nivolumab. That required no specific action. With the second dose, the patient experienced a Grade 2 infusion related reaction that was described as an 'unwell feeling', fever (38.5°C), shaking and tachycardia. The infusion was stopped, the patient hospitalised and treated with intravenous (IV) fluids, IV dexamethasone 40 mg, IV prednisone 100 mg, ranitidine, dimetindene, and acetaminophen. The event was reported as resolved the next day and the treatment dose completed at a lower infusion rate. A further 22 doses have been administered without recurrence of the infusion related reaction. The patient appears to have been treated with a premedication including prednisolone 25 mg for each of these doses. This patient also developed Grade 1 hypothyroidism during treatment.

8.7.6.14. Possible immune mediated adverse reactions from multiple categories

The SCS provides a table of the number of patients who experienced more than one event within the one category of all causality select AEs. This shows that very few patients experience repeated events within the one category. However, from the narratives provided (see summaries above and the example below), it is evident that some patients experienced multiple immune mediated events, with these coming from more than one category. A summary of these patients is requested of the sponsor (see Question 33: Patients with multiple select AEs in Section 11, below).

Example of patient with select AEs from multiple categories

One patient developed a Grade 2 infusion related reaction with the first dose that was treated with intravenous corticosteroid and epinephrine but apparently without interruption of the infusion. This patient subsequently developed a Grade 2 rash following the fourth dose. This was treated with topical anti-fungal and topical corticosteroid medications. Some 16 days later, oral prednisolone was commenced at 10 mg daily with this tapered and ceased during the next 30 days. The rash persisted but was reported to have improved 50 days after it commenced and then to have resolved 80 days after it commenced. During the corticosteroid taper and after dose 8 of nivolumab, the patient was diagnosed with Grade 2 pneumonia that was treated with antibiotic and inhaled bronchodilators. Two weeks later, a CT scan showed pneumonitis. The patient was diagnosed with pneumonitis several days later (after the dose 9 of nivolumab) due to cough and dyspnoea. This was considered drug related and the patient commenced a course of high dose corticosteroids. These were continued for the next 150 days, with the dose appearing to fluctuate between prednisone 15 to 30 mg daily. During this time the patient also developed Grade 1 and then Grade 2 hypothyroidism that did not require specific treatment. The patient also developed a cardiac arrhythmia, not described.

8.7.7. Complications of allogeneic stem cell transplant (allo-SCT)

There were 5 patients in Study CA209039 who discontinued study drug to undergo allo-SCT. At the time of the interim analysis, 4 had died from complications of the allo-SCT. Two of these 4 patients had developed GVHD. In Cohort B of Study CA209205, 6 patients elected to stop the study drug and proceeded to SCT (allo-SCT: n = 5, ASCT: n = 1). Acute GVHD was reported in 3 subjects (Grade 1 or 2). All 6 subjects were alive at the time of the interim analysis. At the time of the interim analysis, there were no patients in Cohort A or C who had ceased nivolumab for subsequent SCT.

The issue of GVHD and other complications of allo-SCT undergone after treatment with nivolumab are discussed further in Section 8.10.7 Safety in patients undergoing allo-SCT after nivolumab therapy and in Question 36: Safety with subsequent allogeneic stem cell transplant.

8.8. Laboratory tests

Comment: These will be presented as reported for the individual studies given that rates as reported for the integrated cHL in the SCS may under-represent rates that may be generalisable to the target population for reasons discussed above.

8.8.1. Liver function

Hepatic function was assessed through serum chemistry laboratories (AST, ALT, ALP, and total bilirubin) and review of AEs related to hepatic function abnormalities.

8.8.1.1. Study CA209205

Cohort B

Increases in hepatic parameters were primarily Grade 1 or 2 with Grade 3 abnormalities reported in ≥ 2% of patients limited to ALT (2.5%), ALP (6.3%), and AST (3.8%). No Grade 4 hepatic parameters or Grade 3 or 4 total bilirubin values were reported.

The number of patients who experienced a ≥ 2-grade shift from Baseline to a Grade 3 or 4 laboratory abnormality was 2 patients for ALP (Grade 3), 3 patients for AST (Grade 3), and 2 patients for ALT (Grade 3).

No patients had concurrent ALT or AST elevation > 3 x ULN with total bilirubin > 2 x ULN within 1 day of last dose of study therapy, or concurrent ALT or AST elevation > 3 x ULN with total bilirubin > 2 x ULN within 30 days of last dose of study therapy.

Cohorts A + C

There were 2 patients who had concurrent ALT or AST elevation > 3 x ULN with total bilirubin > 2 x ULN within 1 day of last dose of study therapy, and 2 patients (0.9%) had concurrent ALT or AST elevation > 3 x ULN with total bilirubin > 2 x ULN within 30 days of last dose of study therapy:

- One patient developed Grade 2 hepatotoxicity on the day of nivolumab dose 6. Treatment with oral prednisolone at 40 mg daily was commenced. The hepatotoxicity was reported to have resolved 12 days later and prednisolone was ceased after a 40 day course. A total of 9 nivolumab doses were administered before this treatment was ceased due to disease progression.
- One patient developed elevated LFTs on the day of nivolumab dose 9. This dose was administered and no specific treatment provided for the abnormal LFTs. These normalised within the next 2 weeks. Nivolumab treatment was continued with a further 3 doses administered prior to DBL. No recurrence of elevated LFTs was reported.

8.8.1.2. Study CA209039

The number of patients who experienced a ≥ 2 grade shift from Baseline to a Grade 3 or 4 laboratory abnormality in either treatment group was: 2 patients for AST (one Grade 3, one Grade 4), 2 patients for ALT (one Grade 3, one Grade 4), and one subject for total bilirubin (Grade 3).

One subject had concurrent ALT or AST elevation > 3 x ULN with total bilirubin > 2 x ULN within 1 day of last dose of study therapy, and concurrent ALT or AST elevation > 3 x ULN with total bilirubin > 2 x ULN within 30 days of last dose of study therapy.

These abnormalities developed on Day 576 of treatment and were associated with intra- and extra-hepatic bile duct dilatation to the level of the Sphincter of Oddi (the patient had had prior cholecystectomy). The abnormalities resolved three days later without treatment and are suggestive of passage of a duct stone. The patient continued on nivolumab for a further 100 days without recurrence.

8.8.2. Kidney function

8.8.2.1. Study CA209205

All cohorts

The majority of patients with at least 1 on-treatment measurement had normal creatinine values during the treatment reporting period, with these all Grade 1 or 2. Shifts in grade from baseline were also limited to Grade 1 or 2 creatinine increases.

8.8.2.2. Study CA209039

All subjects with at least 1 on-treatment measurement had normal creatinine values during the treatment reporting period and there were no abnormalities reported.

8.8.3. Haematology

8.8.3.1. Study CA209205

Abnormalities in haematology tests performed during treatment or within 30 days of last treatment dose were primarily Grade 1 or 2 in all cohorts.

Grade 3 or 4 abnormalities reported in ≥ 5% of patients were:

- Decreased lymphocytes and decreased neutrophils in Cohort B
- Decreased lymphocytes in all cohorts.

A small number of patients in Cohort A + B + C (and Cohort B alone) experienced a ≥ 2-grade shift from Baseline to a Grade 3 or 4 laboratory abnormality:

- 2 subjects with decreased haemoglobin (Grade 3)
- 5 subjects with decreased platelet count (3 with Grade 3)
- 5 subjects with decreased leukocytes (4 with Grade 3)
- 4 subjects with decreased lymphocytes (3 with Grade 3)
- 8 subjects with decreased absolute neutrophil count (5 with Grade 3)

8.8.3.2. Study CA209039

Abnormalities in haematology tests performed during treatment or within 100 days of last treatment dose were primarily Grade 1 or 2. The most common Grade 3 or 4 haematological abnormality was a decrease in absolute lymphocyte count (9 (39.1%) for Grade 3 and no Grade 4).

There were 10 patients who experienced ≥ grade shift from baseline to a Grade 3 or 4 abnormality:

- 2 subjects with decreased haemoglobin (Grade 3)
- 2 subjects with decreased platelet count (1 Grade 3, 1 Grade 4)
- 3 subjects with decreased leukocytes (1 Grade 3, 2 Grade 4)
- 1 subject with decreased lymphocytes (Grade 3)
- 2 subjects had decreased absolute neutrophil count (1 Grade 3, 1 Grade 4).

8.8.4. Thyroid Function Tests

8.8.4.1. Study CA209205

Around 60% of patients had normal TFTs at Baseline in all cohorts.

There were 9 patients in Cohort B who had normal TSH at Baseline and who subsequently had elevated TSH. Of these, 5 patients also had decreased FT3/FT4 results. In all cohorts, there were 29 patients who had normal TSH at Baseline and who subsequently had elevated TSH. Of these, 12 patients also had decreased FT3/FT4 results.

There were 2 patients in Cohort B who had normal TSH at Baseline and who subsequently had decreased TSH. One of these patients also had an elevated FT3/FT4. In all cohorts, there were 8 patients who had normal TSH at Baseline and who subsequently had decreased TSH. Of these, 2 patients also had elevated FT3/FT4 results.

8.8.4.2. Study CA209039

The majority of subjects had normal TSH levels at Baseline and throughout the treatment period.

There were 5 patients who had normal TSH at Baseline and who subsequently had elevated TSH. Of these, 2 patients also had decreased FT3/FT4 results.

There were 2 patients who had normal TSH at Baseline and who subsequently had decreased TSH. FT3/FT4 results were missing for both of these patients.

8.8.5. Pregnancy Tests

8.8.5.1. Study CA209205

Pregnancy tests were negative during the study in all randomised female subjects in Cohort A and Cohort B of childbearing potential. One female subject in Cohort C had a positive pregnancy test during treatment. 11 days after the ninth infusion, the patient was hospitalised for an induced termination of pregnancy after an ultrasound confirmed pregnancy. Treatment with nivolumab was subsequently resumed.

8.8.5.2. Study CA209039

Pregnancy tests were negative during the study in all randomised female subjects of childbearing potential.

8.8.6. Vital signs

8.8.6.1. Studies CA209205 and CA209039

Vital signs were monitored and recorded at the site per institutional standard of care during each infusion of nivolumab visit. Pulse oximetry was obtained at cycle visits for all cohorts. These assessments were not required to be captured in the CRF and were intended to be used as safety monitoring by the treating physician.

8.9. Post-marketing experience

8.9.1. Periodic Benefit-Risk Update Reports (PBRER)

There have been three Periodic Benefit-Risk Update Reports (PBRER) provided to the TGA since approval of nivolumab. These are dated as follows:

1. 4 July 2014 to 3 July 2015
2. 4 July 2015 to 3 January 2016
3. 3 January 2016 to 4 July 2016

The first two PBRERs were reviewed as part of the clinical evaluation for the indication of advanced renal cell cancer. A Periodic Safety Update Report (PSUR) Review for the PSUR dated July 2015 to January 2016, as performed by the TGA is also available. This review provides information regarding Adverse Event Reports (AERs) in the TGA's Adverse Drug-reaction Reporting System (ADRS) for nivolumab.

8.9.1.1. Actions taken for safety reasons

Section 3 of each report describes Actions taken in the Reporting Period for Safety Reasons. These actions, since IBD, are shown in the following table in chronological order:

Table 63. Actions taken since July 2014 for Safety Reasons

Date	Issue and Action Taken
October 2014	The FDA requested that informed consent forms (ICF) and Investigator's Brochures (IB) be updated to include information regarding a case of fatal myasthenia gravis and fatal sepsis
February 2015	The FDA requested that informed consent forms (ICF) and Investigator's Brochures (IB) be updated to include toxic epidermal necrolysis (TEN), rhabdomyolysis/polymyositis, and encephalopathy
March 2015	The FDA requested that informed consent forms (ICF) and Investigator's Brochures (IB) be updated to include haemophagocytic lymphohistiocytosis (HLH).
June 2015	TEN and encephalitis were identified as ADRs through routine pharmacovigilance

Date	Issue and Action Taken
	signal detection. All RSI documents updated and a Dear Healthcare Providers letter distributed.
August 2015	TEN was added to the Warnings and Precautions section of the Company Core Data Sheet (CCDS).
September 2015	The Japanese regulatory body requested an update to their PI and RMP to include information to include 'excessive immune response', 'Myasthenia gravis, myositis' and 'Colitis, Severe diarrhea' as ADRs and Important Identified Risks.
November 2015	The Japanese regulatory body requested an update to their PI and RMP to include information to include Type 1 Diabetes as an ADR and Important Identified Risk
December 2015	Accrual to Study CA209070 was temporarily suspended due to 5 cases of rapid tumour progression and/or pleural effusion.
December 2015	A safety variation was submitted to the EMA to update the PI and CMI to include TEN and encephalitis. The sponsor committed to perform a cumulative search for all cases of encephalitis for inclusion in the Jan 2016 PBRER
December 2015	The Japanese regulatory body requested an update to their PI and RMP to include Neurological disorder, Renal disorder, Adrenal disorder, Encephalitis, Severe skin disorder and Venous thromboembolism' as ADRs and Important Identified Risks.
2016	The Japanese regulatory body requested an update to their RMP to include cardiac disorder as an Important Potential Risk
January 2016	The sponsor issued an Alert for Proper Use of Drug to healthcare professionals (HCPs) in Japan to raise awareness of the incidence of Type-1 diabetes mellitus, including early detection and treatment of fulminant Type-1 diabetes mellitus attributable to nivolumab following an increase in number of Type 1 diabetes mellitus including fulminant Type 1 diabetes
March 2016	The Therapeutic Goods Administration (TGA) requested the addition of Stevens-Johnson syndrome (SJS) event to the AUS Product Information (AUPI) label
March 2016	The TGA requested the sponsor to issue a DHCP letter regarding SAEs, including deaths (1 case of pneumonitis and 1 case of toxic epidermal necrolysis (TEN)), have been reported in a Novartis sponsored Phase II, non-randomized study of nivolumab in combination with an investigational third generation tyrosine kinase inhibitor (TKI). The DHCP letter issued by the sponsor informed HCPs in Australia that the approved indication for Opdivo in locally advanced or metastatic SQ and NSQ NSCLC does not include combination with TKIs and recommended that in patients transitioning from an EGFR-TKI to nivolumab monotherapy, a sufficient wash-out period should be observed to minimize the risk of AEs occurring from the combination. Clinical judgement should be used to determine if any serious or clinically relevant AEs occurring from an EGFR-TKI are resolved prior to initiation of Opdivo.
May 2016	A number of regulatory bodies requested assessment of myositis, myocarditis and rhabdomyolysis events. The Company Corporate Data Sheet (CCDS), Investigator's Brochure (IB), and the RMP were updated to include myocarditis, myositis and rhabdomyolysis as ADRs.
June 2016	The TGA requested a DHCP letter related to influenza vaccine administration in conjunction with nivolumab plus ipilimumab combination regimen. The DHCP letter issued by the sponsor notified HCPs of isolated cases of SAEs in the Northern Hemisphere (including life-threatening or fatal myocarditis, myositis and rhabdomyolysis), in patients administered nivolumab plus ipilimumab combination regimen and who had also received an influenza vaccine and informed the general practitioners (via a template letter from the oncologist or patient) that patients either currently receiving the nivolumab plus ipilimumab combination regimen or those in whom this combination is being considered, of the potential benefits and risks of the

Date	Issue and Action Taken
	effects of the influenza vaccine and nivolumab plus ipilimumab combination regimen.

During the most recent reporting period (January to July 2016), there have been 2 clinically significant revisions made to the nivolumab CCDS. The nivolumab CCDS dated 24 May 2016 was revised to include:

4. A new safety concern of rare, observed cases of SJS and TEN, some with fatal outcome, and described the recommended management guidance for these events. The important identified risk of 'immune-related rash' was renamed as 'immune-related skin ARs'
5. Myocarditis, myositis, and rhabdomyolysis were also added as ADRs under 'other immune-related ARs' given the biological plausibility of the nivolumab mechanism of action to cause or contribute to autoimmunity and the potential inflammatory nature of myocarditis, myositis, and rhabdomyolysis.

Comment: From the above, the safety concerns of fatal myasthenia gravis, toxic epidermal necrolysis (TEN), rhabdomyolysis, myositis, encephalitis, myocarditis have been identified since IBD.

8.9.1.2. Estimated exposure

The PBRERs provides the following estimate of cumulative patient exposure to nivolumab. The PBRER acknowledges some limitations in the estimates of post-marketing use.

Table 64. Cumulative estimated exposure to nivolumab since IBD

	To January 2016 (PBRER 2)	To July 2016 (PBRER 3)
Sponsor's clinical trials	11,038	14,081
EAP/compassionate use programs	13,286	17,348
Post marketing exposure	14,232	36,640
Total	38,556	68,069

Comment: There has been a rapid increase in the cumulative number of patients exposed through post-marketing use: from 1870 for the 12 month period from July 2014 to July 2015, to 14,232 for the 6 month period from July 2015 to January 2106 and to 36,640 for the most recent 6 months, Jan to July 2016. The evaluator notes that, according to the RMP, there is one post-marketing surveillance study of nivolumab monotherapy planned with the objectives to estimate the incidence rates and severity of immune related AEs and to describe the management and outcomes of CTCAE Grades 2 to 5 immune related AEs. According to the study protocol, this will recruit 1200 patients, only from the tumour types of melanoma and NSCLC, and will not be complete for 8 years. Given the number of patients exposed to nivolumab through post-marketing use, it would seem feasible to recruit a larger number and to report the results within a few years. See Section 11.3 for comments on clinical aspects of post-marketing requirements.

8.9.1.3. ADR reports from post-marketing sources

In the reporting interval (4 January 2016 through 3 July 2016), a total of 8,001 events (5,302 serious and 2,699 non-serious) have been reported from the combined post-marketing sources.

Table 65. ADRs from post-marketing sources by reporting period

Reporting period	Estimated patient number exposed	ADR reports		
		Serious	Non-serious	Total
4 July 2014 to 3 July 2015	1870	457	211	668
4 July 2015 to 3 January 2016	12,362	1950	1085	3035
4 January 2016 to 3 July 2016	22,408	5302	2699	8001

From an appendix, numbers of adverse drug reactions by term from post marketing sources in PBRER 3**,** the most frequently reported serious events (≥ 10 from either post-marketing source) are shown in the table below.

Table 66. Most frequently reported[1] serious ADRs from post-marketing sources for the reporting period January 2016 to July 2016

	Spontaneous, Regulatory Authority and Literature	Non-interventional post marketing study and reports from other solicited sources
Progression or treatment failure		
malignant neoplasm progression	284	142
therapeutic response decreased	43	14
drug ineffective	19	13
metastases to central nervous system	34	3
Respiratory, thoracic and mediastinal disorders (all reports)	**405**	**385**
Acute respiratory distress syndrome/acute respiratory failure/respiratory failure	24	5
pneumonitis	106	40
interstitial lung disease	75	193
lung disorder	14	7
alveolitis/allergic alveolitis/diffuse alveolar damage/organising pneumonia	9	20
dyspnoea	51	26
pleural effusion	22	13
pneumonia	37	27
Pulmonary embolism	13	10
haemoptysis	10	6
lower respiratory tract infection/lung infection	10	12
radiation pneumonitis	2	10
Hepatic and biliary disorders (all reports)	**137**	**89**

	Spontaneous, Regulatory Authority and Literature	Non-interventional post marketing study and reports from other solicited sources
autoimmune hepatitis/hepatitis/hepatitis acute	39	15
drug induced liver injury/hepatotoxicity	11	6
hepatic failure	8	2
ALT increased	3	25
AST increased	2	17
Gastrointestinal (all reports)	**259**	**222**
colitis	64	41
diarrhoea	50	68
Ascites	11	2
pancreatitis	15	7
vomiting	8	12
Renal and urinary disorders (all reports)	**76**	**26**
Acute kidney injury	10	7
nephritis/tubulointerstitial nephritis	15	5
renal failure	16	4
renal impairment	14	5
Musculoskeletal and connective tissue disorders (all reports)	**133**	**52**
arthralgia	13	4
arthritis	14	4
back pain	14	3
myalgia	12	2
myositis	11	5
rhabdomyolysis	12	4
headache	10	4
Cardiac (all reports)	**88**	**29**
cardiomyopathy	10	0
myocardial infarction	11	1
myocarditis	13	2
Nervous system disorders (all reports)	**178**	**95**
Myasthenia gravis/myasthenic syndrome	16	7

	Spontaneous, Regulatory Authority and Literature	Non-interventional post marketing study and reports from other solicited sources
confusional state/delirium	13	6
encephalitis	13	6
Guillain-Barre syndrome	3	2
Seizure	11	2
Skin and subcutaneous tissue (all reports)	**104**	**80**
Rash/rash generalised/rash maculopapular	31	32
SJS/TEN/toxic skin eruption	7	5
Haematological		
anaemia	14	12
Neutropaenia	11	3
thrombocytopaenia	20	0
transfusion	13	3
Infusion related and hypersensitivity		
infusion related reaction	32	23
anaphylactic reaction/anaphylactoid reaction/anaphylactic shock	13	1
hypersensitivity	9	4
Endocrine (all reports)	**142**	**125**
hyperthyroidism	54	56
hypothyroidism	25	10
thyroiditis	12	3
diabetes mellitus	19	5
diabetic ketoacidosis	21	6
fulminant type 1 diabetes mellitus	5	3
type 1 diabetes mellitus	15	9
adrenal insufficiency	14	22
hypophysitis	12	11
Other		
uveitis	14	8
pyrexia	36	
chills	10	4
fatigue	13	15

	Spontaneous, Regulatory Authority and Literature	Non-interventional post marketing study and reports from other solicited sources
malaise	11	
weight decreased	11	13
general physical health deterioration	14	6
sepsis	16	13
MODS/CRS/SIRS	6	2
GVHD	3	0
Kidney transplant rejection	3	0
Death	308	32
[a] ≥ 10 reports from either source or event of interest (GBS, GVHD, MODS/SIRS/CRS); Note that some PTs have been moved from their usual SOC for ease of interpretation.		

According to the PBRER: '*A total of 1,134 fatal cases were reported during the reporting period from the combined post-marketing sources. The cause of death for the majority of the fatal cases was associated with complications of the underlying disease/disease progression or was not reported.'* There was no further information provided regarding these patients.

Comment: The most commonly reported ADRs in this table are consistent with the immune-related AEs described in the section above. Respiratory ADRs were reported most frequently, followed by gastro-intestinal, neurological, endocrine, musculoskeletal and skin.

8.9.1.4. Clinically significant safety findings identified during the reporting period from completed and ongoing clinical trials

Two studies were completed in the reporting period, a Phase II study investigating nivolumab 3 mg/kg given Q2W or Q3W sequentially with ipilimumab in advanced or metastatic melanoma (Study CA209064) and an open label Phase III study of nivolumab monotherapy in recurrent or metastatic SCC of the head and neck (Study CA209141). According to the PBRER, there were no new safety concerns with nivolumab monotherapy identified. There were 2 deaths due attributed to nivolumab by the investigator in the second study, one from pneumonitis and one from hypercalcaemia.

There were interim reports for 4 ongoing studies: Studies CA209205, ONO453807, ONO453814 and ONO453815. Study CA209205 is described in the efficacy and safety sections of this document. The others are early phase studies investigating the use of nivolumab monotherapy in oesophageal cancer, recurrent solid tumours (Korean patients), and recurrent non-Hodgkin lymphoma. According to the PBRER, there were no new safety concerns with nivolumab monotherapy identified in these studies.

8.9.1.5. Medication errors

During the reporting period, the company received 261 cases (239 HPC-confirmed cases and 22 non-HPC cases) suggestive of a medication error. In the previous reporting period there were 69 cases. The large difference is attributed to a different search strategy by the sponsor. Of the errors described, most related to improper product storage (n = 60), product use issue (n = 50), inappropriate schedule of drug administration (n = 37), prescribed underdosing (n = 35), underdosing (n = 16) and overdose (n = 13). There were small numbers of concerning errors including incorrect route of administration (n = 2), wrong drug administered (n = 1) and incorrect drug administration duration or rate (n = 8).

8.9.1.6. Lack of efficacy in controlled clinical trials

'*For the purposes of this PBRER, lack of efficacy is defined as failure to demonstrate a statistically significant improvement in the primary efficacy endpoint(s) with nivolumab versus comparator in a randomized controlled trial*.' According to the PBRER, a review did *'not identify any new information suggesting a potential lack of efficacy of nivolumab in treated patients.'*

Comment: Database lock for the PBRER was 3 July 2016 with late-breaking information for up to 28 days after this date included in the PBRER. On 5 August 2016, a press release on the sponsor website announced that '*CheckMate -026, a trial investigating the use of Opdivo (nivolumab) as monotherapy, did not meet its primary endpoint of progression-free survival in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed PD-L1 at = 5%.'*

8.9.1.7. Summary of safety concerns

The following list is provided in the PBRER as shown in Table 67, below.

Table 67. Summary of safety concerns as listed in PBRER 3

Summary of safety concerns (PBRER 3)	
Important identified risks	Immune related pneumonitis Immune related colitis Immune related hepatitis Immune related nephritis and renal dysfunction Immune related endocrinopathies Immune related skin adverse reactions Other immune related adverse reactions Severe infusion ractions
Important potential risks	Embryofetal toxicity Immunogenicity Cardiac arrhythmias (previously treated melanoma indication; EU only)
Important missing information	Paediatric patients (< 18 years of age) Patients with severe hepatic or renal impairment Patients with autoimmune disease Patients already receiving systemic immunosuppressants before starting nivolumab Potential effect of influenza vaccine on safety risks to patients treated with nivolumab or with the combination regimen

Comment: This list of Safety Concerns differs from the list provided in the sponsor's EU-RMP Version 6.0, with the term 'Immune related skin adverse reactions' replacing 'Immune-related rash' and the inclusion of 'Potential effect of influenza vaccine on safety risks to patients treated with nivolumab or with the combination regimen' as Important Missing Information.

Different documents provided by the sponsor provide different lists of Other Immune-related Adverse Reactions

- In a table of the PBRER, the Important Identified Risks of 'Other Immune related Adverse Reactions' are listed as uveitis, pancreatitis, demyelination, GBS, myasthenic syndrome, encephalitis, and myositis.
- Version 4.0 of the PI, as available on the TGA website in August 2016, list Other Immune-related adverse reactions as pancreatitis, uveitis, demyelination, autoimmune neuropathy

(including facial and abducens nerve paresis), Guillain-Barré syndrome, hypopituitarism, myasthenic syndrome, encephalitis, myositis, myocarditis and rhabdomyolysis. The additional immune related ARs of gastritis, sarcoidosis, and duodenitis are described with combination therapy.

- Version 2.2 of the PI provided with this submission lists demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, hypopituitarism, myasthenic syndrome, and encephalitis. As with Version 4.0, the additional immune related ARs of gastritis, sarcoidosis, and duodenitis are described with combination therapy.
- In the EU-RMP Version 6.0 the list of other immune- elated adverse reactions includes pancreatitis, uveitis, demyelination, Guillain-Barre syndrome, and myasthenic syndrome, but not hypopituitarism, myositis, myocarditis, rhabdomyolysis, although it does describe an 'event of special interest' of SIRS.

The evaluator is concerned by the grouping of these assorted reactions under 'Other immune related Reactions' for several reasons:

1. Given that many of these 'Other Immune-related Reactions' have been associated with fatal outcome, greater prominence should be afforded to each of these conditions in the listing of *Important Identified Risks.*
2. The use of the grouped term without an accompanying list of conditions reduces clarity and may result in confusion due to differences in lists across the sponsor's documentation, resulting from different versions and different timetables for updating documents.
3. The use of this grouping means that the identification of new risks with potentially fatal outcome such as myocarditis, myositis, and rhabdomyolysis in the most recent reporting period, are not classed as 'new safety concerns'.

The evaluator therefore recommends that any table of identified risks, potential risks, and missing information associated with the use of nivolumab provided in the sponsor's documentation (RMP, PBRER) explicitly lists the individual conditions grouped together as 'Other Immune related Adverse Reactions'.

8.9.1.8. Signal evaluation

Four new signals (3 closed and 1 ongoing) were evaluated during the reporting period.

- Myositis, myocarditis, and rhabdomyolysis
- Association between the events of myositis, myocarditis and rhabdomyolysis, and the influenza vaccine in patients receiving nivolumab therapy
- Complication of allogeneic haematopoietic stem cell transplantation (HSCT) after nivolumab therapy
- Pneumonitis, interstitial lung disease, and lung infiltration with overlapping use of nivolumab and marketed TKIs.

Myositis, myocarditis and rhabdomyolysis

This signal evaluation was prompted by a request for information by the FDA following a suspected unexpected serious adverse reaction (SUSAR) reporting the events of myocarditis and myositis related to nivolumab and ipilimumab from Study CA209218. During the review process, BMS also decided to review rhabdomyolysis.

A high level summary of this review was provided in the PBRER. This stated that '*the frequency of myocarditis observed in phase 1-3 clinical trials is 0.18% with nivolumab + ipilimumab combination therapy, which is comparable to the background rate (range 0.01% - 0.12%)'* and that '*Given the biological plausibility of the mechanism of action of nivolumab to cause or contribute to autoimmunity and the potential inflammatory nature of myocarditis,*

immunotherapy and nivolumab + ipilimumab combination therapy may be a possible causal factor associated with myocarditis'. The same conclusion was drawn for myositis and rhabdomyolysis. As a result, '*Myositis, myocarditis, and rhabdomyolysis have been added to the RMP and CCDS as ADRs and continue to be monitored as Product Specific Monitored Events (PSMEs)'.*

Comment: A more comprehensive review titled 'Nivolumab Injection for Intravenous Infusion, Clinical Overview to support label update with Stevens-Johnson Syndrome, Toxic epidermal necrolysis, myositis, myocarditis and rhabdomyolysis' was provided to the TGA during the evaluation of the safety of a related submission. This described search strategies, relevant case reports identified and a comparison of rates in nivolumab treated patients to the prevalence in cancer patients in general. The same conclusions were drawn in the review as those stated in the PBRER. In a TGA evaluation of this review it was noted that each of these ADRs had been associated with fatal outcome and it was recommended that this be explicitly stated in the PI. It was also recommended that the warning box in the nivolumab PI include nivolumab monotherapy. The conclusion drawn in the evaluation was that '*the evaluator agrees that in the population currently being treated with nivolumab (patients with difficult to treat and poor prognosis metastatic cancer), the overall benefit-risk profile is not substantially changed by the identification of these potentially fatal risks. However, minimising the risks from these potentially fatal irARs requires appropriate wording in the warning box and appropriate educational materials that are immediately accessible by clinicians.'*

8.9.1.9. Association between the events of myositis, myocarditis and rhabdomyolysis, and the influenza vaccination while receiving nivolumab treatment

This signal evaluation was prompted by the receipt of 3 SUSAR cases (received mid-late December 2015 to January 2016) that reported events of life threatening or fatal myocarditis, myositis and/or rhabdomyolysis in patients with a common history of having received an influenza vaccine before initiation or during nivolumab and ipilimumab therapy. These reports also prompted the TGA's request for DHCP letter in June 2016 (see Table 63. Actions taken since July 2014 for safety reasons).

A high level summary of the review was provided in the PBRER. This stated that '*the Company determined that the current clinical and safety data are insufficient to issue any specific recommendation or communication regarding whether getting influenza vaccination whilst receiving nivolumab indeed increases the risk of myositis, myocarditis or rhabdomyolysis.'* The PBRER also notes that the potential effect of influenza vaccine on safety risks to patients treated with nivolumab or with the combination regimen has been added as important missing information and that this will be monitored through routine pharmacovigilance activities.

Comment: Due to the lack of detail provided in the summary, the evaluator is unable to evaluate these conclusions.

Complications of allogeneic HSCT after nivolumab therapy

As described above, a number of patients in Studies CA209205 and CA209039 developed complications of allogeneic SCT after nivolumab treatment. According to the PBRER, '*the FDA mandated in May 2016 that the USPI should include Complications of Allogeneic HSCT after Opdivo in Warnings and Precautions Section 5.10* and a *Post-Marketing Requirement (PMR) in order to characterize complications after allogeneic HSCT following nivolumab therapy, in at least 90 patients with cHL and to evaluate toxicities for at least 180 days after allogeneic HSCT*'. According to the PBRER, this was based on biological plausibility.

The signal of complications of allogeneic HSCT post-nivolumab was evaluated by the sponsor. A high level summary of this signal evaluation was provided in the PBRER. This recognised that '*Anti-PD1 immunotherapy carries biological plausibility to contribute to developing complications post-allogeneic HSCT'.* The results of the evaluation were summarised as *'the frequency (15/34, 44.1%) of GVHD post-allogeneic HSCT in CA209205 and CA209039 is similar to the background*

rate (49.6%; cHL). The allogeneic HSCT related-mortality (5/34, 14.7%) in CA209205 and CA209039 is within the range of population-based studies (6-36%, cHL). There was 1 case of hepatic VOD (1/34, 2.9%) and that is lower than the background rate (9.4%, cHL).' The conclusion drawn by the sponsor was that '*GVHD and hepatic VOD post-allogeneic HSCT are not ADRs for nivolumab'.*

Comment: Due to the lack of detail provided in the summary, the evaluator is unable to evaluate these conclusions. This potential risk is the subject of a clinical question (see Question 36: Safety with subsequent allogeneic stem cell transplant in Section 11, below) and is also discussed further below in Section 8.10.9.

Pneumonitis, ILD, and lung infiltration with combination use of nivolumab and marketed TKIs

This signal evaluation was prompted by the reports of 7 cases of ILD that have been reported among patients with NSCLC in whom treatment with EGFR-TKIs was started completion of nivolumab therapy. Three of the 7 cases had a fatal outcome; the contributory role of both nivolumab and the EGFR-TKIs on ILD could not be ruled out. These reports also prompted the TGA's request for a DHCP letter in March 2016 (see Table 63. Actions taken since July 2014 for safety reasons, above).

According to the PBRER, this signal evaluation is ongoing. No further information was provided.

8.9.2. Australian post-marketing experience

Nivolumab was approved for use in Australia by the TGA in January 2016. No estimate of the use of nivolumab in Australia since approval by the TGA is provided by the sponsor. Of note is that nivolumab is listed on the Pharmaceutical Benefits Scheme (PBS) for Unresectable Stage III or Stage IV malignant melanoma (with strict criteria) and not for NSCLC.

A search of the publically available TGA's Database of Adverse Event Notifications (DAEN) in September 2016 found that there had been 2 reports of adverse events, involving 2 patients, prior to January 2016. Both cases occurred in clinical trials, one case had the MedDRA term of 'death' and the other was of renal failure, urosepsis and death. A search for reported events after approval until the most recent available date (from 16 January 2016 to 18 May 2016) found 44 reports of adverse events. In 10 of these cases, the reported outcome was death. The most common reports were of disease progression (n = 8), pneumonitis (n = 6) and hypersensitivity (n = 4). MedDRA terms with death as an outcome are shown in Table 68 below, noting that multiple terms could be used for each patient.

Table 68. MedDRA terms with death as an outcome

MedDRA reaction term	Number of cases	Number of cases where death was a reported outcome
Disease progression	8	4
Pneumonitis	6	3
Myocarditis	2	1
Multiple organ dysfunction syndrome	1	1
Respiratory failure	1	1
Skin discolouration	1	1
Stevens-Johnson syndrome	1	1
Acute myocardial infarction	1	1
Cerebrovascular accident	1	1

MedDRA reaction term	Number of cases	Number of cases where death was a reported outcome
dermatitis bullous	1	1
Stevens Johnson Syndrome	1	1
Hypotension	1	1
Liver function test abnormal	1	1
Lower respiratory tract infection	1	1

For some of these patients, the terms used are given in Table 69, below.

Table 69. MedDRA terms used and medications taken by each patient

Medicine(s) taken by patient	MedDRA Terms used
Nivolumab	Dermatitis bullous, hypotension, liver function test abnormal, lower respiratory tract infection, skin discolouration, Stevens Johnson syndrome.
Nivolumab and ipilimumab	Colitis
Nivolumab	Myocarditis, pneumonitis
Nivolumab	Pneumonitis
Nivolumab	Infusion related reaction, pyrexia
Nivolumab	Confusional state, headache, inflammation, seizure
Nivolumab	Myocarditis
Nivolumab	Cerebrovascular accident
Nivolumab	Diarrhoea, Toxic epidermal necrolysis
Everolimus and nivolumab	Acute myocardial infarction, MODS, respiratory failure, disease progression

A periodic safety update review was performed by the TGA. This review provides an update to the number of adverse events reported for nivolumab and shows an additional 21 reports between May 2016 and July 2016:

- 'As of 6 July 2016, the TGA has received 65 Adverse Event Reports (AERs) in the Adverse Drug-reaction Reporting System (ADRS) for nivolumab, including 14 deaths. 54 cases were sole-suspected for nivolumab, 10 cases were suspected for both nivolumab and ipilimumab and in 1 case both nivolumab and everolimus were both suspected. 33 patients were male and 22 patients were female with ages ranging from 55 to 87 years (gender was not specified in 10 reports and age was not specified in 19 reports).
- Adverse events reported in ADRS in patients receiving nivolumab include, but are not limited to:

– Gastrointestinal disorders: pancreatitis, vomiting projectile, constipation, diarrhoea, gastric dilatation, colitis, gastritis, mouth ulceration, intestinal obstruction, dry mouth, nausea and abdominal pain

- Skin and subcutaneous tissue disorders: hyperhidrosis, skin discolouration, rash, Stevens-Johnson syndrome, dermatitis bullous, pruritis, toxic epidermal necrolysis and vitiligo
- Respiratory, thoracic and mediastinal disorders: lower respiratory tract disorders, pneumonitis, pleural effusion and respiratory failure
- Vascular disorders: hypotension, cerebellar haemorrhage, pulmonary embolism, angina pectoris, cerebrovascular accident, reversible cerebral vasoconstriction syndrome, cerebral infarction and haemorrhage intracranial
- Cardiac disorders: myocarditis, dyspnoeas, stress cardiomyopathy and acute myocardial infarction
- Immune system disorders: autoimmune haemolytic anaemia, hypersensitivity and cytokine release syndrome
- Blood and lymphatic system disorders: leukaemoid reaction, myelodysplastic syndromes, haemolysis, thrombocytopaenia and neutropaenia
- Hepatobiliary disorders: cholestasis and hepatitis
- Renal and urinary disorders: urinary retention and incontinence
- Nervous system disorders: seizure, confusional state, dysarthria and headache
- Infections and infestations: oral candidiasis'.

8.10. Safety issues with the potential for major regulatory impact – immune related adverse reactions

Immune mediated ADRs have been identified as 'Important identified risks' in the sponsor's RMP and in the PBRERs. These have been grouped into organ related categories, with the remaining listed under 'Other immune related adverse reactions'. Many of these ADRs have been associated with fatal outcome. Early recognition with management by dose delay or discontinuation of nivolumab, and the administration of high dose corticosteroids in more severe cases, is recommended to improve outcome.

The evaluators and Delegates of previous nivolumab submissions have noted the proactive monitoring for these complications in the clinical trials, with extensive laboratory testing and pulse oximetry at rest and with exertion performed prior to each dose. Similarly stringent monitoring recommendations are not included in the PI, raising the concern that this may result in opportunities for early detection for these complications being missed and that the safety profile reported in the clinical trial setting may not translate to the post-approval setting. Also of concern is that the full PI is not distributed as a package insert, limiting access by clinicians to the important information contained within this document. The evaluator notes that, despite training and access to an Investigators Brochure, it is evident in some of the narratives provided in Study CA209205 that immune related AEs were not considered early by the investigator and that delays occurred in the commencement of corticosteroid therapy, with this potentially worsening outcome.

Descriptions of immune mediated ARs as Important identified risks: The descriptions of immune mediated ADRs provided in the PBRER appears to be limited to those reported in registrational studies, with no reference made to post-marketing sources or other studies in the sponsor's clinical trial programme. According to the descriptions provided, there have been no Grade 5 events in any of the categories of immune mediated adverse reaction. Cumulative reviews of event categories provided by the sponsor, in other PBRERs and an SRR, have identified patients who have died from AEs that potentially immune mediated and considered likely or possibly related to nivolumab therapy, including deaths from TEN, encephalitis, pneumonitis, myasthenia gravis, myositis, myocarditis, and rhabdomyolysis.

The evaluator of a previous nivolumab submission also noted that:

'In general, these reactions appear to be mild (Grade 1 or 2) although more severe reactions, including fatalities have been reported. The following deaths have been attributed to immune mediated adverse reactions in patients receiving nivolumab:

- *5 due to study drug related pneumonitis reported in Study CA209003*
- *1 due to pneumonitis in a patient also receiving ipilimumab in Study CA209069*
- *1 due to entero-colitis and pancreatitis in a patient also receiving ipilimumab in Study CA209004*
- *1 due to encephalitis in Study CA209057*
- *1 due to pneumonitis in Study CA209063.*

The following descriptions of these reactions have been sourced from tables of the most recent PBRER. This has been supplemented with information from the narratives of IMAE provided in the CSRs of Studies CA209039 and CA209205 and cumulative reviews described in earlier PBRERs and the SRR. The number of post-marketing reports of serious ADRs for the reporting period January 2016 to July 2016 is shown in Table 66, above.

8.10.1. Immune related pneumonitis

From the PBRER:

Of the 1991 patients who have received nivolumab monotherapy, any grade pneumonitis has been reported in 3.1% of this population, with Grade 3 or 4 in 0.8% and no Grade 5. These rates were approximately double in the 448 patients receiving nivolumab + ipilimumab.

Most subjects treated with corticosteroids had complete resolution of the pulmonary event within days to weeks. Subjects with more severe cases have been difficult to treat. In the minority of cases, subjects that did not initially respond to corticosteroids were administered additional immunosuppressants (for example infliximab) with resolution in some cases.

As documented in previous CERs of nivolumab submissions, there have been a number of deaths due to pneumonitis, with this attributed to nivolumab, in the clinical trial programme: 5 in Study CA209003 (a dose escalation study) and 1 in a patient also receiving ipilimumab in Study CA209069. Pneumonitis, and other respiratory PTs consistent with an immune basis, have been a common source of post-marketing serious ADR reports (see Table 66, above). The narratives from the studies in this submission show that the diagnosis of pneumonitis may be delayed and that some patients may have a prolonged and relapsing course.

8.10.2. Immune related colitis

From the PBRER:

Of the 1991 patients who have received nivolumab monotherapy, any grade colitis has been reported in 13.3% of this population, with Grade 3 or 4 in 1.4% and no Grade 5. These rates were 45.5% and 15.8% respectively in the 448 patients receiving nivolumab + ipilimumab.

Grade 1 or 2 events were treated symptomatically and Grade 3 or 4 events were treated with systemic corticosteroids or with additional immunosuppressant agents for events that were refractory to steroid treatment. Delayed dosing or permanent discontinuation of therapy was required in subjects with Grade 3 or 4 events or in subjects with Grade 2 events that were not improving with symptomatic management.

The narratives from the studies in this submission show that diarrhoea due to colitis may persist for many months, despite corticosteroid steroid courses and discontinuation of nivolumab.

1.1.2. Immune related hepatitis

From the PBRER:

Of the 1991 patients who have received nivolumab monotherapy, any grade hepatitis has been reported in 6.9% of this population, with Grade 3 or 4 in 1.9% and no Grade 5. These rates were 27.9% and 16.7% respectively in the 448 patients receiving nivolumab + ipilimumab.

Most subjects had complete resolution of the hepatic event following treatment according to the management guideline. In the minority of cases, subjects that did not initially respond to corticosteroids were administered additional immunosuppressants (for example, mycophenolate mofetil) with resolution

The narratives from the studies in this submission show that hepatitis may require prolonged courses of corticosteroids.

The safety signal of Drug Induced Liver Injury was evaluated in the first PBRER (dated July 2014 to July 2015) at the request of the FDA. This has been described in the Round 2 evaluation report for the Nivolumab RCC submission as follows:

'There were 16 potential DILI cases identified by laboratory criteria (concurrent AST or ALT > 3 x ULN and TB > 2 x ULN). The majority of these cases had additional potential confounding risk factors (baseline liver metastases, concomitant medications with known hepatotoxicity, abnormal liver tests at Baseline, or concurrent medical conditions). Two cases (<0.1%, 2/3994) had ALP < 2 x ULN without other causes and met Hy's Law criteria:

- *1 case occurred with nivolumab + ipilimumab combination treatment. The patient improved after stopping study drugs and treatment with corticosteroids*
- *1 case occurred with sequential ipilimumab followed by nivolumab treatment. Study drug was stopped and the patient was treated with steroids and MMF and the event resolved*

Review of the case management for all 16 cases confirmed that the hepatotoxicity cases were manageable using the established hepatic AE management guideline with 14/16 responding to the treatment with favourable outcomes. As hepatotoxicity was already an identified risk of nivolumab, no changes were made to the CCDS or RMP.'

8.10.3. Immune related nephritis and renal dysfunction

From the PBRER:

Of the 1991 patients who have received nivolumab monotherapy, any grade nephritis and renal dysfunction has been reported in 3.0% of this population, with Grade 3 or 4 in 0.5% and no Grade 5. These rates were 4.2% and 1.6% respectively in the 448 patients receiving nivolumab + ipilimumab.

Most subjects had complete resolution of the renal event following treatment according to the management guideline

8.10.4. Immune related endocrinopathies

From the PBRER:

For the 1991 patients who have received nivolumab monotherapy, reported incidence rates were:

- Any Grade: adrenal disorder 0.5%, thyroid disorder 8.7%, diabetes 0.2%, and pituitary disorder 0.3%
- Grade 3 or 4: adrenal disorder 0.2%, thyroid disorder < 0.1%, diabetes < 0.1%, and pituitary disorder 0.2%
- Grade 5: 0

For the 448 patients receiving nivolumab + ipilimumab, reported incidence rates were:

- Any Grade: adrenal disorder 3.3%, thyroid disorder 23.7%, diabetes 0.4%, and pituitary disorder 8.9%
- Grade 3 or 4: adrenal disorder 1.3%, thyroid disorder 1.6%, diabetes 0.2%, and pituitary disorder 1.8%
- Grade 5: 0

Endocrinopathies are manageable with hormone replacement and/or steroid treatment. Lifelong hormone replacement may be required.

Endocrinopathies were a common source of post-marketing ADR reports.

8.10.5. Immune related skin ARs

From the PBRER:

Of the 1991 patients who have received nivolumab monotherapy, any grade skin AR has been reported in 26.7% of this population, with Grade 3 or 4 in 1.0% and no Grade 5. These rates were 63.4% and 7.4% respectively in the 448 patients receiving nivolumab + ipilimumab.

8.10.5.1. SJS and TEN

TEN was identified as an ADR of nivolumab in the first PBRER (July 2014 to July 2015). At that time, according to the CER for a previous nivolumab submission 3 cases were identified: 2 of the cases had received confounding medications; one fatal case had a close temporal relationship between nivolumab monotherapy and onset.

A cumulative review for Stevens-Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN) was provided with the SRR evaluation for a previous nivolumab submission. This review included all sources (clinical trials, EAP, post-marketing, published literature and solicited) and is summarised in the CER for that submission. There were 20 case reports identified, with 12 reported as SAEs of SJS and 8 reported as SAEs of TEN, 16/20 receiving nivolumab monotherapy and 5/20 of the cases had fatal outcome. From the limited information available, severity did not appear to be greater with combination therapy, in fact more deaths from SJS/TEN occurred with monotherapy. The review reported an estimated frequency of SJS is 0.03% with nivolumab monotherapy and 0.03% with nivolumab + ipilimumab combination therapy in the sponsor's clinical trials (including EPA programs). The estimated frequency of TEN is 0.01% with nivolumab monotherapy, and 0.03% with nivolumab + ipilimumab combination therapy.

8.10.6. Other immune related adverse reactions

From the PBRER:

For the 1991 patients who have received nivolumab monotherapy, reported incidence rates were:

- Any Grade: Uveitis 0.5%, pancreatitis 0.4%, demyelination < 0.1%, GBS < 0.1%, myasthenic syndrome < 0.1%, encephalitis < 0.1%, myositis < 0.2%
- Grade 3 or 4: Uveitis 0, pancreatitis 0.2%, demyelination < 0.1%, GBS < 0.1%, myasthenic syndrome < 0.1%, encephalitis < 0.1%, myositis < 0.1%
- Grade 5: 0

For the 448 patients receiving nivolumab + ipilimumab, reported incidence rates were:

- Any Grade: Uveitis 1.3%, pancreatitis 0.9%, Guillain-Barre syndrome 0.4%, encephalitis 0.2%, myositis < 0.2%
- Grade 3 or 4: Uveitis 0.2%, pancreatitis 0.7%, Guillain-Barre syndrome 0.4%, encephalitis 0.2%, myositis < 0.2%
- Grade 5: 0

Most of the events were reversible according to the management guideline. In the minority of cases, subjects that did not initially respond to corticosteroids were administered additional immunosuppressants (for example, IVIg) with resolution. Discontinuation of nivolumab is required in subjects with high-grade events.

Cumulative reviews for a number of these 'Other immune related adverse reactions' are available.

8.10.6.1. Encephalitis

An updated review of encephalitis is provided in each of the PBRERs, as per the request of the EMA's PRAC. Up to April 2015, there had been 5 cases of encephalitis reported and in the PBRER July 2015 to January 2016, there had been 16 cases reported. For the most recent reporting period, January to July 2016, 28 serious cases were had been reported. These were reported as: encephalitis (n = 26), limbic encephalitis (n = 1), and encephalitis autoimmune (n = 1). There were 13 spontaneous, 9 clinical trial, 5 Phase IV/solicited and 1 literature (post-marketing) case.

Of the 28 cases:

- The reports came from the US, Europe, Japan and Israel.
- 19 were reported in patients who received treatment with nivolumab monotherapy and 9 were reported in patients who received treatment with nivolumab in combination with ipilimumab.
- The patients were aged from 27 to 85 years and the time of onset from 5 to 222 days.
- 24/28 were assessed as related to nivolumab including 2 two cases with fatal outcome. Of these fatal cases, one was with nivolumab monotherapy and one was in combination with ipilimumab.
- In 12 cases, the outcome was unknown, in 9 cases the outcome was reported as Recovered/Resolved and in 4 as Not Recovered/Not Resolved.
- There were 3 patients with Grade 3 severity who were treated with high dose steroids, the outcome for these patients was reported as resolved in 2 and not resolved in the third. One patient who developed encephalitis during nivolumab + ipilimumab combination therapy was treated with corticosteroids and the event resolved. However, after completion of the steroid taper, the patient was hospitalised with encephalitis. The patient had a total of 4 episodes of encephalitis and died.

8.10.6.2. Neurological SAEs

A cumulative review of serious neurological reports was included in a PBRER 1 and is summarised in the Round 2 CER for the submission to the TGA to approve nivolumab for RCC): the review found '*30 events that were reported as possibly related to nivolumab monotherapy or nivolumab + ipilimumab. These included:*

- *6 cases of Guillain-Barre syndrome or Miller Fisher syndrome with 1 case occurring with nivolumab monotherapy, one with combination therapy, one with sequential therapy and 2 with 'blinded therapy'. Treatment included high-dose corticosteroids and IVIg (4), IVIg (1), or corticosteroids and plasmapheresis (1) with outcomes of resolved in 4, resolving in 1 and resolved with sequelae in 1. The overall frequency was 0.1% (6/5244). 2 cases of Paraneoplastic limbic encephalitis in 63 treated patients with SCLC receiving nivolumab monotherapy*
- *a number of other neurological events (not described)'*

8.10.6.3. Myasthenia gravis

A cumulative review of this was provided in PBRER 1. This was summarised in the Round 2 CER for the submission to approve nivolumab for RCC):

'A cumulative review of myasthenia gravis identified 4 confirmed serious cases. Two cases occurred with nivolumab monotherapy and two with combination therapy with ipilimumab. Study drugs were discontinued in all 4 cases and the patients were treated with steroids (4/4), cholinesterase inhibitors (3), plasmapheresis (1), and intravenous immunoglobulin (3). Patient outcomes were recovered (1), recovering (1), not resolved at the time of death due to disease progression (1), and death due to myasthenia gravis complicated with sepsis (1). The assessment was that myasthenic syndrome/myasthenia gravis is considered as an ADR of nivolumab (estimated frequency <0.1%, 4/5244) and was added to the 'Other Immune-Related Adverse Reactions' category in the CCDS and RMP'.

8.10.6.4. Myositis and rhabdomyolysis

A cumulative review for myositis and rhabdomyolysis was provided with the SRR evaluation. This review included all sources (clinical trials, EAP, post-marketing, published literature and solicited) to April 2016 and is summarised in the CER for that submission.

The myositis review identified 34 cases of myositis, with all events considered related to nivolumab. Of the 34 cases, 27 patients received nivolumab monotherapy, and 7 received therapy with nivolumab + ipilimumab. Event outcomes were reported as fatal in 3 cases, 2 of these patients were receiving nivolumab monotherapy.

The rhabdomyolysis review identified 13 cases, 10 of whom received nivolumab monotherapy and 3 received nivolumab + ipilimumab. All events were considered related to nivolumab. There were 4 cases with fatal outcome, 3 of these patients were receiving nivolumab monotherapy.

8.10.6.5. Myocarditis

A cumulative review for myocarditis was provided with the SRR evaluation. This review included all sources (clinical trials, EAP, post-marketing, published literature and solicited) to April 2016 and is summarised in the CER for that submission.

The review identified 18 cases, 10 of whom received nivolumab monotherapy and 8 received nivolumab + ipilimumab. All events were considered related to nivolumab. There were 6 cases with fatal outcome, 1 of these patients was receiving nivolumab monotherapy.

8.10.7. Severe infusion reaction

The following is from the PBRER.

Of the 1991 patients who have received nivolumab monotherapy, any grade severe infusion reaction has been reported in 5.4% of this population, with Grade 3 or 4 in 0.4% and no Grade 5. These rates were 3.8% and 0% respectively in the 448 patients receiving nivolumab + ipilimumab.

Comment: A higher rate of infusion reactions were reported in Study CA209205 than have been reported with other tumour types. This is attributed to a high incidence at one investigational site without further explanation.

Anaphylaxis and anaphylactic shock have been reported as serious ADRs from post-marketing sources.

8.10.8. Safety in patients undergoing Allo-SCT after nivolumab treatment

Allo-SCT is an important treatment option for patients with relapsed/recurrent cHL as it is the only potentially curative treatment option currently available.

At the time of the interim analyses of Studies CA209205 and CA209039, there were 12 patients who discontinued nivolumab treatment to undergo SCT – allo-SCT n = 10; ASCT n = 2. Of the 10 patients undergoing subsequent allo-SCT, 5 were from Cohort B of Study CA209205 and 5 were from Study CA209039. Allo-SCT in these patients appears to have been performed as consolidative treatment (in patients who achieved a response with nivolumab) or as rescue

treatment (in patients who either failed to achieve a response to nivolumab or who developed progressive disease despite an initial response).

The outcomes of these patients are shown in the table below. Of the 10 patients receiving allo-SCT, 4 had died at the time of database lock for the interim analyses and 5 had developed GVHD.

Table 70. Outcome of patients receiving SCT after nivolumab treatment

Type of SCT	Date of Last Nivo. Dose	Date of SCT	GVHD (Onset Date)	Infections & Infestations (Onset Date)	IMAEs (Onset Date)	Death
allo-SCT	06-Mar-2015	16-Apr-2015	Grade 1 acute (18-Jun-2015)	-	-	-
allo-SCT	05-Feb-2015	05-Mar-2015	Grade 2 acute (24-Mar-2015)	-	-	-
allo-SCT	23-Mar-2015	29-Apr-2015	-	-	-	-
allo-SCT	17-Mar-2015	17-Apr-2015	Grade 1 acute (04-Jun-2015)	-	-	-
allo-SCT	12-May-2015	04-Jun-2015	-	-	-	-
ASCT	07-May-2015	29-May-2015	-	-	-	-
allo-SCT	02-Dec-2013	16-Jan-2014	-	-	-	-
allo-SCT	25-Oct-2013	21-Nov-2013	-	-	-	Disease (05-Dec-2014)
allo-SCT	14-Nov-2013	24-Dec-2013	Grade 2 acute (11-Jan-2014)	Grade 2 staphylococcal infection (16-Jan-2014); Grade 2 pneumonia (27-Jan-2014); Grade 4 lung infection (24-Nov-2014; > 100 days after last dose)	-	Pulmonary compromise (05-Dec-2014)
allo-SCT	29-Jul-2013	08-Aug-2013	Grade 3 acute (09-Sep-2013) (Gr 5 > 100 d after last dose)	Grade 3 encephalitis (19-Sep-2013), Grade 4 bacteriemia (18-Oct-2013)	-	SCT complications, GVHD, infection (23-Nov-2013)
allo-SCT	16-Dec-2013	19-Mar-2014	-	-	-	SCT complications (27-Jul-2014)
ASCT	31-Oct-2013	19-Nov-2013	-	Grade 1 skin infection (20-Nov-2013), Grade 1 vaginal infection (20-Nov-2013), Grade 2 urinary tract infection (01-Dec-2013)	Grade 3 pneumonitis (30-Jan-2014)	-

Note: Each row represents a single patient. Patient identifiers have been removed.

In the SCS, the sponsor states: '*Although the numbers are small, acute graft-versus-host disease (GVHD) and infectious complications in nivolumab-treated patients receiving subsequent SCT were consistent with historical data in SCT patients. In addition, limited data does not suggest any complication that would indicate diagnosis of hepatic veno-occlusive disease (VOD)/hepaticsinusoidal obstruction syndrome (SOS).*'

Despite this conclusion by the sponsor, the following advice has been included in the 'Warnings and Precautions' of the FDA approved label and in the subsequent explanatory section 5.10:

> *'Complications of allogeneic HSCT after Opdivo: Monitor for hyperacute graft-versus-host-disease (GHVD), Grade 3-4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated adverse reactions. Transplant-related mortality has occurred. (5.10)'*
>
> *'5.10 Complications of Allogeneic HSCT after Opdivo:*
>
> *Complications, including fatal events, occurred in patients who received allogeneic HSCT after Opdivo. Outcomes were evaluated in 17 patients from Trials 8 and 9 who underwent allogeneic HSCT after discontinuing Opdivo (15 with reduced-intensity conditioning, two with myeloablative conditioning). The median age at HSCT was 33 (range: 18 to 56), and a median of 9 doses of Opdivo had been administered (range: 4 to 16). Six of 17 patients (35%) died from complications of allogeneic HSCT after Opdivo. Five deaths occurred in the setting of severe or refractory GVHD. Grade 3 or higher acute GVHD was reported in 5/17 patients (29%). Hyperacute GVHD, defined as GVHD occurring within 14 days after stem cell infusion, was reported in 2 patients (20%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (35%) within the first 6 weeks post-transplantation, with five patients responding to steroids. Two cases of*

encephalitis were reported: one case of Grade 3 lymphocytic encephalitis without an identified infectious cause, which occurred and resolved on steroids, and one case of Grade 3 suspected viral encephalitis which was resolved with antiviral treatment. Hepatic veno-occlusive disease (VOD) occurred in one patient, who received reduced-intensity conditioned allogeneic SCT and died of GVHD and multi-organ failure. Other cases of hepatic VOD after reduced-intensity conditioned allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. Cases of fatal hyperacute GVHD have also been reported.

These complications may occur despite intervening therapy betweeb PD-1 blockade and allogenic HSCT.

Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.'[30]

The evaluator notes that the FDA approved label refers to 17 patients who received allogeneic SCT following nivolumab. The SCS as provided in this submission refers to 10 patients. The sponsor is asked to provide an updated cumulative review of patients who have been received allo-SCT after prior nivolumab treatment, including any patients who have received intervening therapy/therapies (see Question 36: Safety with subsequent allogeneic stem cell transplant in Section 11, below).

The evaluator also notes the FDA post market requirement to characterise the safety of allo-SCT in patients who have received prior nivolumab treatment for cHL.

Figure 24. Post-approval requirement by the FDA for the indication of cHL

Requirement/Commitment Number: 2

Required Under:	FDAAA Section 505(o)(3)
Original Projected Completion Date:	12/31/2022
Description:	Characterize complications after allogeneic hematopoietic stem cell transplantation (HSCT) following nivolumab in at least 90 patients with classical Hodgkin lymphoma, of which at least 50% had received nivolumab alone or in combination as the regimen immediately prior to the allogeneic HSCT conditioning regimen. Evaluate toxicities at least through transplant Day 180, and include details of prior nivolumab treatment and the transplant regimen. Characterize toxicities including hyperacute graft-versus-host disease (GVHD), severe (grade III-IV) acute GVHD, febrile syndromes treated with steroids, immune mediated adverse events, pulmonary complications, hepatic veno-occlusive disease, critical illness, and transplant-related mortality. Toxicities may be characterized prospectively, or through a combination of prospective and retrospective data analysis.
Current Status:	Pending

8.11. Other safety issues

8.11.1. Distribution of the Product Information

If the approach of a 'Pack Leaflet' is to be implemented, it is essential that the full PI is immediately accessible to prescribers, pharmacists and other health professionals. The proposed pack leaflet correctly states that it is an abbreviated version of the complete PI and that the complete PI should be referred to before prescribing. However, no description of how the full PI is to be distributed has been provided, nor are any directions provided in the pack leaflet for locating the complete PI. Clinical staff who are accustomed to accessing this information through the package insert, therefore, may be unable to access the full PI. This poses a significant safety risk.

8.11.2. Safety related to drug-drug interactions and other interactions

No information provided.

[30] US PI dated May 2016. Accessed at the sponsor's website July 2016 Trial 8 is Study CA209205, Trial 9 is Study CA209039.

8.11.3. Safety in special populations

8.11.3.1. Safety in patients aged 65 years or more

The following comparison of safety related events across age-groups is provided in the Clinical Overview (see Table 71 below). Data is derived from clinical studies for the indications of cHL, RCC, melanoma, and NSCLC. The frequency of SAEs, AEs leading to dropout and postural hypotension appear to increase in older age (aged > 65 years). There were no patients aged 75 years or more in the cHL group and only 7 aged between 65 and 74 years.

Table 71. Comparison of on-treatment AEs by age group

	Number of Subjects (%)			
	Monotherapy Data Integrated Across Indications[a]			
MedDRA Terms	Age < 65 years (N = 1301)	Age 65-74 years (N = 504)	Age 75-84 years (N = 165)	Age 85+ years (N = 21)
Total AEs	1260 (96.8)	492 (97.6)	162 (98.2)	21 (100.0)
Serious AEs -Total	501 (38.5)	236 (46.8)	82 (49.7)	12 (57.1)
Fatal	104 (8.0)	45 (8.9)	21 (12.7)	3 (14.3)
Hospitalization/prolong existing hospitalization	445 (34.2)	209 (41.5)	73 (44.2)	8 (38.1)
Life-threatening	20 (1.5)	7 (1.4)	2 (1.2)	0
Cancer	13 (1.0)	11 (2.2)	9 (5.5)	1 (4.8)
Disability/incapacity	1 (<0.1)	1 (0.2)	0	0
AEs leading to drop-out	153 (11.8)	77 (15.3)	38 (23.0)	5 (23.8)
Psychiatric disorders	222 (17.1)	78 (15.5)	26 (15.8)	6 (28.6)
Nervous system disorders	449 (34.5)	180 (35.7)	57 (34.5)	13 (61.9)
Accidents and Injuries	88 (6.8)	46 (9.1)	14 (8.5)	3 (14.3)
Cardiac disorders	113 (8.7)	51 (10.1)	13 (7.9)	5 (23.8)
Vascular disorders	195 (15.0)	91 (18.1)	26 (15.8)	9 (42.9)
Cerebrovascular disorders	9 (0.7)	9 (1.8)	1 (0.6)	1 (4.8)
Infections and infestations	493 (37.9)	215 (42.7)	62 (37.6)	10 (47.6)
Anticholinergic syndrome	439 (33.7)	160 (31.7)	56 (33.9)	9 (42.9)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	128 (9.8)	68 (13.5)	24 (14.5)	4 (19.0)

[a] Includes nivolumab monotherapy data from studies CA209039, CA209205, CA209025, CA209063, CA209017, CA209057, CA209037, CA209066, and CA209067 (monotherapy arm only).
MedDRA Version: 18.0; CTC version 4.0 (except for Study CA209004: CTC version 3.0).
Includes events reported between first dose and 30 days after last dose of study therapy.
Abbreviations: AE: adverse event; HLGT: MedDRA High-Level Group Term; MedDRA: Medical Dictionary for Regulatory Activities; SMQ: Standardized MedDRA Queries; SAE: serious adverse event; SOC: System Organ Class.

The annotated PI (version 2.2) provided with this submission includes the following advice for dosing in the elderly in the 'Special Populations' section of the 'Dosage and Administration' section:

> *'Elderly patients:*
>
> *No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). No dose adjustment is required for elderly patients (≥ 65 years) (see section Pharmacokinetics).'*

The information provided in the PI is not consistent with the information in the Table 71 (from the SCS) above, which indicates a higher rate of SAEs (including those with fatal outcome) and AEs resulting in discontinuation in patients aged more than 65 years, and that these rates increase further with advanced age. The evaluator is of the opinion that additional information regarding the elderly should be included in the 'Special Populations' section and that the statement on page 74 should be reworded. The evaluator recommends the following:

Under Special Populations:

- *'Elderly Patients:*

A higher incidence of serious adverse events, including deaths, have been reported in elderly patients (age >65 years), with this increasing further in advanced age (75-84 years). This should be taken into account in determining the individual benefit-risk for elderly patients.'

Under Special Populations:

· 'Elderly patients:

No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). No dose adjustment is required for elderly patients (≥ 65 years) (see section Pharmacokinetics). Analysis of AEs in nivolumab monotherapy has found that the rate of reported SAEs increases with increasing age, from age 65 years.'

8.11.3.2. Safety in Pregnancy

Pregnancy was an exclusion criterion for the clinical studies and was pro-actively monitored for in women of child-bearing age. Overall there have 3 pregnancies in female subjects: 2 in patients treated with nivolumab monotherapy (n = 843) and one in patients treated with nivolumab in combination with ipilimumab (n = 162) in clinical trials. One of these pregnancies was in a patient with cHL in Study CA209205; this patient had an elective termination and resumed nivolumab treatment. One other case is reported to have had an ectopic pregnancy. The outcome was not reported for the third case.

The Australian PI Version 4.0 contains the following advice in the section 'Special Populations':

'Use In Pregnancy (Category D):

Opdivo is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk. Advise females of reproductive potential to use effective contraception during treatment with Opdivo for at least 5 months following the last dose of Opdivo.

There are no data on the use of Opdivo in pregnant women. Human IgG4 is known to cross the placental barrier and Opdivo is an IgG4; therefore Opdivo has the potential to be transmitted from the mother to the developing foetus. It is not known whether ipilimumab can cause fetal harm when administered to a pregnant woman.

The effects of Opdivo on prenatal and postnatal development were evaluated in monkeys that received Opdivo at 10 and 50 mg/kg twice weekly from the onset of organogenesis in the first trimester through delivery, at exposure levels 8 and 35 times, respectively, those observed at the clinical dose of 3 mg/kg of Opdivo (based on AUC). There was a dose-dependent increase in fetal losses and increased neonatal mortality mainly in the 3rd trimester of pregnancy and after birth.

The remaining offspring of Opdivo -treated females survived to scheduled termination, with no treatment-related clinical signs, alterations to normal development, organ-weight effects, or gross and microscopic pathology changes. Results for growth indices, as well as teratogenic, neurobehavioral, immunological and clinical pathology parameters throughout the 6-month postnatal period were comparable to the control group.'

8.12. Evaluator's overall conclusions on clinical safety

The target population for the main part of the proposed indication is: patients with relapsed or refractory classical Hodgkin lymphoma (cHL) following after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. The target population for the second part of the indication is: patients with relapsed or refractory classical Hodgkin lymphoma (cHL) following at least two prior therapies in patients who are not candidates for ASCT.

The sponsor's assessment of safety is based on the safety results from 2 open label single arm, multiple cohort studies:

- Study CA209039 was a Phase I study that included 23 patients with cHL. This included a sub-group of 15 patients (the ASCT-Bren Failed group) who had failed both ASCT followed by brentuximab vedotin. The other 8 patients had either not received ASCT or not received brentuximab vedotin. All patients were followed for a median of 23 months (minimum 18 months). During this time, the ASCT-Bren Failed group received a median of 24 doses of nivolumab for a median duration of treatment of 12 months with 2/15 patients still on treatment at the time of the analysis. The other 8 patients received a median of 13 doses with 1/8 patients still on treatment at the time of analysis. The most common reasons for treatment discontinuation for the 20 patients was progressive disease (n = 6) or patient request/other (n = 6 with 5/6 electing to undergo SCT).
- Study CA209205 was a Phase II study with multiple cohorts, with recruitment to the cohorts occurring at different times and rates:
  - Cohort B comprised 80 patients who had failed both ASCT followed by brentuximab vedotin as salvage therapy, with the interim analysis performed after a minimum follow-up of 6 months (median follow-up of 8.9 months). The median duration of treatment was not reached; the median number of doses received was 17. At the time of the interim analysis, 51/80 patients were continuing treatment with nivolumab. Of the 29 who had discontinued treatment, the most common reason was disease progression (n = 13).
  - Cohort A included 63 patients who had relapsed following ASCT but who had not received brentuximab vedotin. Analysis of this cohort is due to occur after a minimum follow-up of 12 months. At the time of the interim analysis, the minimum follow-up was 1 month and the median duration of follow-up was 5 months. During this time, the patients received a median of 11 doses of nivolumab. At the time of the interim analysis, 54/63 patients were continuing treatment with nivolumab.
  - Cohort C included 97 patients who had relapsed following ASCT but who had not received brentuximab vedotin. Analysis of this cohort is due to occur after a minimum follow-up of 12 months. At the time of the interim analysis, the minimum follow-up was 1 week and the median duration of follow-up was 2.8 months. During this time, the patients received a median of 6 doses of nivolumab. At the time of the interim analysis, 90/97 patients were continuing treatment with nivolumab.

The sponsor has combined the patients from these two studies to create an 'integrated cHL' population for the purpose of the safety analysis presented in the Summary of Clinical Safety (SCS). Of the 263 patients in this population, 160 (61%) are from Cohort A and C of CA209205. The sponsor has noted that, '*Compared with CA209205 Cohort B and CA209039 all cHL, the safety profile for patients in CA209205 Cohort A or Cohort C may not be as adequately characterized at these database locks due to the shorter extent of follow up in these cohorts.'* The evaluator agrees with the sponsor that the safety profile of Cohort A and C is not adequately characterised and notes that the sponsor's Exposure-Response Safety analysis has indicated that the occurrence of AEs appears to be related to duration of treatment. This is confirmed by the lower rate of AEs reported in Cohort A and C compared to Cohort B and Study CA209039. The evaluator is, therefore, of the opinion that the inclusion of Cohort A and C has 'diluted' the safety results presented by the sponsor. This may cause under-estimation of AEs and over-estimation of safety for the proposed population. These concerns may be resolved by the provision of updated safety data that includes an additional 6 to 12 months of follow-up for Cohort A and C (see Question 26: Updated safety analysis of adverse events in Section 11, below).

To better enable generalisability to a post-approval population, the assessment of the safety of nivolumab in patients with cHL provided by the evaluator is based on the findings of the individual Study CA209039 and Cohort B of Study CA209205, although information from Cohort A and C has been used to capture rare events. The integrated Summary of Clinical Efficacy (SCE) population will also be referred to: this consists of the 15 patients from Study CA209039 and the 80 patients from Cohort B of Study CA209205 who had relapsed cHL

following ASCT and then brentuximab vedotin. The assessment is further supplemented with information from post-marketing use.

8.12.1. Adverse Events

The two studies show that AEs occur in almost all patients receiving nivolumab. The most common AEs were fatigue, pyrexia, cough, nausea, diarrhoea and rash, although there were some differences in rates across the two studies: the higher rates were reported in Study CA209039 are consistent with a longer duration of treatment. The presence of these AEs did not appear to impact on QoL, according to the mean results of the measures used in Study CA209205 (see Results for other outcome measures for this study in Section 7, above).

Table 72. Most common AEs (all causality) by PT in Study CA209039 and Cohort B of Study CA209205

	Study CA209039 all cHL, n = 23		Study CA209205 Cohort B, n = 80	
	Any Grade	Grade 3, 4	Any Grade	Grade 3, 4
Preferred Term (%)				
Total number with an AE	23 (100)	13 (56.5)	79 (98.8)	32 (40.0)
Fatigue	12 (52.2)	1 (4.3)	29 (36.3)	0
Pyrexia	11 (47.8)	0	25 (31.3)	0
Cough	14 (60.9)	0	22 (27.5)	0
Diarrhoea	11 (47.8)	1 (4.3)	22 (27.5)	0
Nausea	7 (30.4)	0	19 (23.8)	0
Vomiting	7 (30.4)	0	13 (16.3)	1 (1.3)
Upper respiratory tract infections	6 (26.1)	0	19 (23.8)	0
Rash	10 (43.5)	0	17 (21.3)	2 (2.5)
Pruritus	9 (39.1)	0	18 (22.5)	0
Thrombocytopaenia	9 (39.1)	4 (17.4)	2 (2.5)	0
Lymphopenia	5 (21.7)	3 (13.0)	0	0
Hyperglycaemia	9 (39.1)	0	8 (10.0)	1 (1.3)
Hypokalaemia	5 (21.7)	0	6 (7.5)	0
Back pain	5 (21.7)	1 (4.3)	10 (12.5)	2 (2.5)
Arthralgia	4 (17.4)	0	18 (22.5)	0

Headache	**5 (21.7)**	**0**	**9 (11.3)**	**1 (1.3)**
Peripheral neuropathy	**5 (21.7)**	**0**	**10 (12.5)**	**0**

Most of the AEs reported were Grade 1 or 2, although Grade 3 or 4 AEs were reported in 40% and 56.5% of patients in Study CA209039 and Cohort B respectively. SAEs were reported in 25% or 40%. Discontinuation due to study drug toxicity was rare (5 patients) with this due to pancreatitis, myelodysplastic syndrome, Grade 3 or 4 autoimmune hepatitis, Grade 3 or 4 AST/ALT increased and Grade 5 MSOF. Deaths were also uncommon (8 patients) and most commonly attributed to disease progression. However, there was one death due to multiple system organ failure (MSOF) in a Cohort B patient that was attributed to nivolumab toxicity; this was subsequently changed by the investigator after an autopsy revealed a peripheral T-cell lymphoma. There were also 4 deaths in Cohort A and C patients (3 within 30 days of last dose) and one of these deaths was attributed to nivolumab toxicity, a patient who died from multiple organ failure 2 weeks after developing respiratory failure due to *Pneumocystis jiroveci* infection. The narratives of other deaths describe patients with complex illnesses and in whom, for several patients, it is possible that pneumonitis or pleural effusion due to nivolumab contributed to the patient's death. Also of note is that of the 5 deaths in Study CA209039, 4 were in patients who discontinued nivolumab to undergo allo-SCT and who subsequently died from GVHD and other complications of allo-SCT.

Table 73. Summary of AEs in cHL populations

	Study CA209039 N = 23	**Study CA209205 Cohort B** N = 80	**Integrated SCE** N = 95
Total subjects with an event (%)			
All Cause, all grades AEs	23 (100)	79 (98.8)	94 (98.9)
All cause, Grade 3 to 4 AEs	13 (56.5)	32 (40.0)	79 (30.0)
All cause Grade 5 AEs	0	1	1
Drug-related AEs, Grade 3 to 4[a]	5 (21.7)	20 (25.0)	23 (24.2)
Discontinuations due to AEs	2	3	
Serious Adverse Events (SAEs)			
Any grade	8 (40)	20 (25)	26 (27.4)
Grade 3 to 4	5 (33.3)	10 (12.5)	15 (15.8)
Grade 5	0	1 (1.3	1 (1.1)
Deaths	5 (21.7)	3 (3.8)	7 (7.4)
Within 30 days of last dose	0	1(1.3)	1 (1.1)
Within 100 days of last dose	0	1(1.3)	1 (1.1)
Attributed to nivolumab toxicity	0	1[b] (1.3)	1 [b](1.1)
Note: a) the proportion of AEs assessed as drug related was much lower by the investigators of Study CA209039 compared to Study CA209205; b) this attribution was changed to not related after database lock on the basis of the autopsy findings.			

The sponsor has provided a comparison of patients with cHL who receive nivolumab monotherapy to patients with solid tumours who have received nivolumab monotherapy. In this comparison, that uses the integrated cHL population, the use of nivolumab in cHL populations compares favourably to patients with solid tumours, with lower rates of Grade 3 or 4 AEs, SAEs,

and AEs leading to discontinuation. However, if comparison is made to the rates reported in the individual studies and not including Cohort A or C, the rates of the most commonly reported AEs are higher in the cHL population. Comparing the rates of Grade 3 or 4 AEs and SAEs is difficult due to marked disparity in rates between Studies CA209039 and CA209205 (Cohort B). Deaths occurred more commonly with the other tumour types.

Table 74. Comparison to patients with solid tumours

	Study CA209039 N = 23	**Study CA209205** Cohort B N = 80	**RCC** N = 406	**Melanoma** N = 787	**NSCLC** N = 535
Median number of nivolumab doses (min, max)	18 (6, 48)	17(3, 25)	12 (1, 65)	12 (1, 45)	6 (1, 52)
Total subjects with an event (%)					
All Cause, all grades AEs	23 (100)	79 (98.8)	397 (97.8)	768 (97.6)	524 (97.9)
All cause, Grade 3 or 4 AEs	13 (56.5)	32 (40.0)	216 (53.2)	319 (40.5)	244 (45.6)
Drug related AEs, Grade 3 or 4	5 (21.7)	20 (25.0)	76 (18.7)	108 (13.7)	59 (11.0)
Discontinuations due to AEs	2 (13.3)	3 (3.8)	72 (17.7)	91 (11.6)	99 (18.5)
SAEs, all grades	8 (40)	20 (25)	194 (47.8)	319 (40.5)	263 (49.2)
Deaths	5 (21.7)	3 (3.8)	181 (44.6)	251 (31.9)	339 (63.4)
Within 30 days of last dose	0	1(1.3)	19 (4.7)	57 (7.2)	66 (12.3)
Within 100 days of last dose	0	1(1.3)	56 (13.8)	151 (19.2)	181 (33.8)
Attributed to nivolumab toxicity	0	1[b] (1.3)	0	1 (0.1)	2 (0.4)
Most frequently reported AEs, all grades					
Fatigue	12 (52.2)	29 (36.3)	195 (49.0)	328 (41.7)	189 (35.3)
Pyrexia	11 (47.8)	25 (31.3)	67 (16.5)	114 (14.5)	76 (14.2)
Diarrhoea	11 (47.8)	22 (27.5)	96 (23.6)	223 (28.3)	86 (16.1)
Cough	14 (60.9)	22 (27.5)	120 (31.5)	148 (18.0)	154 (28.0)
Nausea	7 (30.4)	19 (23.8)	115 (28.3)	213 (27.1)	117 (21.9)
Pruritus	9 (39.1)	18 (22.5)	75 (18.5)	182 (23.1)	56 (10.5)
Rash	10 (43.5)	17 (21.3)	64 (15.8)	176 (22.4)	60 (11.2)

Interpretation of this comparison is limited by the small numbers of patients with cHL. However, the comparison of safety to the safety in other tumour types is particularly important for two reasons. One reason is that patients with cHL appear to continue on nivolumab treatment for considerably longer than patients with solid tumours, according to the median number of doses. The second reason is that the population PK analysis presented by the sponsor has found that nivolumab clearance is reduced by one third in the cHL population, compared to patients with solid tumours, and that this, in turn, causes a 15 day increase in the half-life and a 43% increase in exposure (as measured by median $C_{avg,ss}$). The frequency with which AEs occur appears to increase with the duration of treatment. The Exposure-Response Analysis (Safety) did not find a relationship between $C_{avg,ss}$ and the rate of AEs but there were some limitations in this analysis. Without more information regarding the rate of AEs in a larger number of patients with cHL the evaluator is unable to conclude that the safety of nivolumab in patients with cHL is

similar to that which has been observed in patients with solid tumours. The sponsor is requested to provide updated information, with this including patients from Cohort A and C after a longer period of follow-up. See Question 27: Updated comparison across tumour types in Section 11, below.

The actual impact of AEs on patients receiving nivolumab monotherapy is difficult to determine. The sponsor has stated that most were Grade 1 or 2, with the implication that there was little impact on the patient. There were two measures of QoL in Study CA209205, the EORTC-QLQ-C30 questionnaire and the EQ-5D VAS. There was a high rate of responses received in the early part of the study but very few responses after Week 33. The average results of both measures were consistent and did not show any worsening of QoL from Week 9 to Week 33 of study participation. Other measures of the impact of AEs tell a somewhat different story. A table of the SCS provides a presentation of SAEs, and their consequences, across age groups in the pooled population of patients receiving nivolumab monotherapy (3mg/kg Q2W). Combining the age groups shows that almost all of the patients in whom an SAE was reported, required hospitalisation (or prolongation of hospitalisation) for that SAE: 41% of patients had an SAE reported and 36.9% required hospitalisation or a prolongation of hospitalisation due to SAE(s). This table also shows that 8.7% of patients had SAE with fatal outcome and were 'life-threatening' in another 1.5% of patients.

Table 75. Impact of SAEs on the integrated population treated with nivolumab monotherapy

	Monotherapy data integrated across indications (n = 1991)
Serious Adverse Events (SAEs), n (%)	n (%)
SAEs, total	831 (41.7)
Fatal	173 (8.7)
Hospitalisation/prolong hospitalisation	735 (36.9)
Life threatening	29 (1.5)
Cancer	34 (1.7)
Disability/incapacity	2 (0.1)

The narratives of SAEs and other AEs provided in the interim CSRs describe patients requiring recurrent hospitalisation and prolonged illnesses. These factors suggest that AEs experienced during nivolumab treatment may have a major effect on patients receiving this treatment, although this is not reflected in the average QoL measures in patients with cHL. Health resource utilisation data was not collected in either of the cHL studies.

8.12.2. Immune mediated adverse events

The major safety concern with nivolumab is immune related adverse events. These are variously referred to by the sponsor as 'select AEs',' Immune mediated AEs (IMAEs)', 'other events of special interest (OESI)' and 'Other IMAEs of special interest'. They are not reported prospectively by the investigators but are identified by a retrospective search of reported AEs. They are, therefore, defined by the grouping of PTs used in the search strategy. Their description is provided as the organ categories of endocrine, GI, hepatic, pulmonary, renal, skin and 'Other' select AE categories. The 'Other' category, at the time of the studies, consisted of demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, pancreatitis, and uveitis.

Immune related AEs appear to be common with nivolumab treatment. There were 98 such AEs reported in the 80 patients in Cohort B and 52 in the 23 patients in Study CA209039. A further

56 were reported in the 63 Cohort A patients and 61 in the 97 Cohort C patients. As with all cause AEs, the number of immune related AEs from the most commonly reported categories of endocrine, gastrointestinal and skin, appears to increase with the duration of nivolumab treatment.

Table 76. Select AEs in Study CA209205 by cohort, and in Study CA209039

	Study CA209205 Cohort B	**Study CA209205** Cohort A	**Study CA209205** Cohort C	**Study CA209039**
Median number of doses	17	11	6	18
Category n (%)	N = 80	N = 63	N = 97	N = 23
Endocrine	14 (17.5)	9 (14.3)	5 (5.2)	5 (21.7)
Gastrointestinal	21 (26.3)	17 (27)	12 (12.4)	11 (47.8)
Hepatic	8 (10)	3 (4.8)	11 (11.3)	9 (39.1)
Pulmonary	1 (1.3)	1 (1.6)	5 (5.2)	2 (13)
Renal	4 (5.0)	2 (3.2)	2 (2.1)	
Skin	33 (41.3)	16 (25.4)	14 (14.4)	14 (60.9)
Hypersensitivity/Infusion Reaction	17 (21.3)	8 (12.7)	12 (12.4)	4 (17.4)
Total select AEs	98	56	61	52

Grade 3 or 4 events reported in the two studies combined included:

- Endocrine: none
- Gastro-intestinal category: 2 patients with diarrhoea, one patient with colitis
- Hepatic category: 10 patients with 13 reports including blood alkaline phosphatase increased (n = 4), ALT increased (n = 4), AST increased (n = 2) and autoimmune hepatitis (n = 1), hepatitis (n = 2), liver function tests abnormal (n = 1)
- Pulmonary category: one patient with one report of acute respiratory distress syndrome, one patient with pneumonitis
- Renal category: one patient with one report of nephritis autoimmune
- Skin category: 4 patients with 4 reports including rash (n = 3) and rash maculopapular (n = 1)
- Hypersensitivity/infusion reaction category: one patient with one report of hypersensitivity.

Events treated with immunosuppression included:

- 6 events of hepatitis
- One event of diarrhoea/colitis
- 6 events of pneumonitis
- 14 events of rash
- 9 hypersensitivity events

The sponsor has provided descriptions of the number of events from each category in each study, the number requiring treatment with immunosuppressive therapy (corticosteroids) and the outcome of the events. The sponsor's conclusion is that most of the events are minor and

well-managed by dose delay and/or immunosuppressive therapy. Other measures of impact on patients (such as time off work or time unable to perform activities of daily living, the number requiring hospitalisation, duration of hospitalisation, the number requiring care in an intensive care unit, the number requiring organ support such as renal replacement therapy or invasive ventilator support) have not been provided. From the table describing SAEs above, and assuming that immune related AEs are the AEs most likely to be reported as SAEs, then up to 40% of patients may require hospitalisation and 8% may die. The narratives provided in the interim CSRs of Studies CA209205 and CA209039 describe a range of illnesses due to immune related AEs. These range from asymptomatic abnormalities in thyroid function tests and liver function tests to patients with diarrhoea that persists for months, despite immunosuppressive therapy and cessation of nivolumab, and patients with recurrent episodes of dyspnoea and hypoxia requiring hospitalisation. Also of note in the narratives are a number of patients in whom an immune-mediated cause of the patient's non-specific illness did not appear to be considered early, resulting in delay in commencement of immunosuppressive therapy with prolongation of the illness and possible worse outcome. The occurrence of this despite investigator training and the provision of an investigator's brochure that describes the presentation and management of immune related adverse events raise concerns regarding how well the safety observed in the clinical trials may translate to wider use.

8.12.3. Post-marketing experience

The PBRERs describe recognition of an increasing number of adverse reactions assumed to be immune mediated. As noted above, the list of 'Other events' at the time of commencement of the above studies (2012 and 2014) was demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, pancreatitis, and uveitis. In the most recent version of the PI available on the TGA's website (pages 56 and 57, dated 1 September 2016, this list now consists of: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, hypopituitarism, myasthenic syndrome, encephalitis, myositis, myocarditis and rhabdomyolysis. The additional immune related ARs of gastritis, sarcoidosis, and duodenitis are described with nivolumab + ipilimumab combination therapy. Of note is that the events of pneumonitis, toxic epidermal necrolysis, Stevens Johnson syndrome, encephalitis, myasthenia gravis, myositis, myocarditis and rhabdomyolysis have each been associated with fatal outcome. The estimated incidence of Grade 3 or 4 events in each of the categories is less than 2%; the estimated incidence of the rarer more serious events such as pancreatitis, encephalitis, myasthenic syndrome, TEN, SJS, GBS, myocarditis, myositis is less than 1%. However, the increasing recognition of a wider variety of AEs with possible immune mediated cause over the past few years suggests that the safety of nivolumab has yet to be fully characterised. It also suggests that immune related AEs were under-recognised in earlier studies, with illnesses and deaths potentially attributed to progressive disease or other causes, such as infection, rather than immune mediated conditions.

Nivolumab was approved for use in Australia in January 2016. Prior to this there had been two notifications of adverse events to the TGA's database. Since January 2016, there have been 63 events notified (53 of nivolumab monotherapy and 10 for combination therapy with ipilimumab). Of the total of 65 events, 14 have had fatal outcome.

8.12.4. Safety in patients undergoing allo-SCT following nivolumab therapy

A new safety concern has been raised in the cHL population with the possibility of an increase in GVHD and other complications of allo-SCT in patients undergoing this treatment following nivolumab therapy. This is a significant concern as allo-SCT is the only treatment option for patients who relapse after autologous SCT that may have a curative effect.

There were 10 patients in Studies CA209039 and CA209205 who ceased nivolumab therapy to undergo allo-SCT, with this performed as consolidative treatment (in patients who achieved a response with nivolumab) or as rescue treatment (in patients who either failed to achieve a response to nivolumab or who developed progressive disease despite an initial response). Another two patients underwent autologous SCT. Of the 10 patients who had undergone allo-

SCT, 4 had died of complications of allo-SCT and 5 had developed acute GVHD at the time of the interim analysis.

Nivolumab received accelerated approval as monotherapy in relapsed cHL following ASCT and brentuximab vedotin from the FDA in May 2016. The FDA-approved label at the time included the Warning that patients receiving allo-SCT after nivolumab should be monitored for hyperacute GVHD, Grade 3 or 4 GVHD, steroid requiring febrile syndrome, hepatic veno-occlusive disease and that transplant mortality has occurred. This was further explained in a later section that described 17 patients from Studies CA209039 and CA209205 who underwent allo-SCT, with 5 deaths occurring in the setting of severe or refractory GVHD; 2 patients with hyperacute GVHD (onset within 14 days of stem cell infusion), 6 patients with steroid requiring febrile syndrome (without identified infective cause), 2 patients with encephalitis and one patient with veno-occlusive disease. This section also noted that other cases of VOD after RIC allo-SCT have been reported in patients who had received a PD-1 receptor blocking agent prior to transplantation and that the complications of allo-SCT may occur despite intervening therapy between the PD-1 receptor blocking agent and allo-SCT.

The most recent PBRER includes a high level summary of a cumulative review of the signal of complications of allogeneic HSCT post-nivolumab. This reports that 15 of 34 patients from Studies CA209039 and CA209205 who underwent allo-SCT after nivolumab therapy experienced GVHD and that 5/34 patients died. The rate of GVHD and transplant related mortality was assessed in this review as within the range of population based studies. The sponsor has been asked to provide an updated cumulative review of patients who have been received allo-SCT after prior nivolumab treatment, including any patients who have received intervening therapy or therapies to enable evaluation of this risk. The sponsor is asked to provide an updated review of patients who undergo allo-SCT following nivolumab treatment (see Question 36: Safety with subsequent allogeneic stem cell implant in Section 11, below).

8.12.4.1. Safety in special populations

Elderly

The sponsor has provided new information in the SCS that the frequency of SAEs (including fatal events and events requiring hospitalisation), AEs leading to dropout, and postural hypotension appear to increase in older age (age > 65 years). This is shown by a comparison across age groups performed using the pooled population. The evaluator recommends that this risk be included in the PI.

Other special populations

No new information has been provided regarding other special populations. The evaluator notes that 'Missing Information', as listed in the most recent PBRER and RMP, include the special populations of:

- Patients with severe hepatic or renal impairment
- Patients with autoimmune disease
- Patients already receiving immunosuppressants before starting nivolumab.

This is noted in the PI, although some recommendations regarding strengthening the information regarding hepatic and renal impairment have been made by the evaluator of a previous RCC-based submission for nivolumab.

Patients with pre-existing interstitial lung disease

Patients with symptomatic interstitial lung disease were excluded from the cHL studies. This is an important exclusion given the first line therapy for cHL includes bleomycin, the reported rate of interstitial lung disease with bleomycin is 10%. The evaluator notes that this information is included in the PI.

Patients with ECOG status > 1

Only patients with ECOG performance status of 0 or 1 were included in the cHL studies presented. The Exposure-Response Safety analysis found that the rate of Grade 3 or 4 AEs was increased in patients with ECOG status of 1 compared to 0. The evaluator recommends that this information be included in the PI.

8.12.5. Conclusions regarding safety

Drawing conclusions regarding the safety of nivolumab in the cHL population is difficult due to the small numbers of patients exposed and the large difference in reported rates of events in the two studies. This difference in rates of AEs may be attributed to the difference in duration of therapy between the two studies; it is notable that comparison of reported rates of AEs across the different cohorts of Study CA209205 and Study CA209039 increase considerably as the duration of treatment increases. The safety of nivolumab observed in patients with solid tumours cannot be extrapolated to patients with cHL due to the much longer duration of therapy observed in cHL patients and the reduced nivolumab clearance.

Almost every cHL patient in Study CA209039 and Cohort B of Study CA209205 experienced at least one AE. Averaging across the two groups, around half experienced Grade 3 or 4 AEs and around one third had SAEs reported. From the analysis of the pooled population provided by the sponsor, around 40% of patients were hospitalised due to SAEs (or had hospitalisation prolonged). Despite these factors, using the measures of the small number of patients who discontinued treatment due to AEs and the proportion of patients who received ≥ 90% of planned dose intensity (76% for Cohort B and 78% for Study CA209039), nivolumab appears to be well tolerated in many patients.

Immune mediated adverse reactions are the major safety concern. These appear to occur commonly, with most cases of mild severity and to respond to dose delay ± immunosuppressive therapy. However, there are patients who have more severe manifestations of these events, requiring hospitalisation and having fatal outcome. In some of these patients, delayed recognition of the immune basis of the illness appears to have resulted in delays in appropriate immunosuppressive therapy, with this potentially worsening outcome (recurrent hospitalisations, potentially contributing to death). Seemingly haphazard administration of corticosteroids was also apparent in some of the narratives provided. This occurred despite the Investigator's Brochure and investigator training; this raises the concern that the safety seen in the clinical trials may not translate to the wider setting unless clinicians are provided with at least similar support and training.

Final conclusions regarding the safety of nivolumab in patients with cHL cannot be drawn by the evaluator at this stage. The 160 patients from Cohorts A and C have had a further 12 months of follow-up since database lock for the interim analysis of Study CA209205. The evaluator notes that later safety related information regarding these patients has been provided to the FDA and has been included in the review of the safety signal regarding allo-SCT in the most recent PBRER. The provision of updated safety results for these patients to the TGA may provide important additional safety information and is indispensable for any final conclusions made by this evaluator regarding the safety of nivolumab in patients with cHL.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Table 77. First round assessment of benefits

Indication: *Opdivo, as monotherapy is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) following autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin*	
Benefits	**Strengths and Uncertainties**
Improvement in ORR in Study CA209205 with: · ORR per IRRC = 53/80, 66.3% (95% CI 54.8, 76.4) ® No with CR = 7/80 ® No with PR = 46/80. · Estimated median duration of response (DOR) 7.8 months (95% CI 6.64, NA). Note: 31/53 responders per IRRC were still on treatment and censored prior to the analysis.	Strength: Clinically meaningful ORR. Uncertainties: · Study design: Open label, non-comparator study with surrogate end-point and results based on outcomes of 80 patients. · Study conduct: Questions regarding study conduct at two sites responsible for treating 21/80 patients. · Low rate of CR (8.8%). Historically, treatments with high CR rates have had better patient outcomes. · Durability of response not known; the estimated DOR of 7.8 months at the time of analysis is unstable due to the number of censored patients. · Translation to improved overall survival not known; median OS not reached during median 9-month follow-up. Median OS in patients with cHL relapsing after ASCT with current therapies estimated at approximately 2 years. · Clinical importance of the results; historically ORRs of 50 to 70 have been reported for a number of treatment options in r/R cHL, together with median DORs of 5 to 7 months.
Improvement in ORR in Study CA209039 with: · ORR of 60% in comparable group ® No with CR= 0/15 ® No with PR = 9/15. · Estimated median duration of response 12 months (95% CI 1.8, NA).	Strengths: · ORR result consistent across the two studies. · Estimated median DOR clinically meaningful. Uncertainties: · Open label, non-comparator study with surrogate endpoint and results based on a group of 15 patients with cHL who have received prior ASCT followed by brentuximab vedotin who were recruited by chance. · Retrospective analysis of tumour response by IRRC following late protocol amendment. · No patient achieved CR.
Future studies to confirm the results of these early studies.	Uncertainty: Confirmatory study The sponsor has provided written advice to the TGA that no confirmatory studies are planned: [The sponsor] *'has not*

Indication: *Opdivo, as monotherapy is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) following autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin*	
Benefits	**Strengths and Uncertainties**
	conducted nor is planning a confirmatory Phase III study in this precise patient population due to the small number of patients available, the late stage of disease and the absence of an approved comparator.'

Table 78. First round assessment of benefits

Indication: *Opdivo, as monotherapy is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) following at least two prior therapies in patients who are not candidates for ASCT.*	
Benefits	**Strengths and Uncertainties**
There were 5 patients in Study CA209039 who had not received prior ASCT. Of the 5 ASCT naïve patients, 4 had an objective response to nivolumab, with BOR per IRRC of CR (n = 3), PR (n = 1) and SD (n = 1).	Uncertainties: · Given the small number of patients, determining benefit in this patient population requires generalisation from other patients with cHL. This may suggest clinically relevant tumour response but has not demonstrated any more meaningful benefits, such as increased PFS or OS. · Current phrasing of this part of the indication would allow nivolumab to be used instead of the more established brentuximab vedotin.

The two studies presented for efficacy were a Phase I and Phase II study. Both were exploratory, single arm, open label, multiple cohort studies, with one cohort from each study relevant to the proposed indication. The sponsor has noted that relapsed/refractory HL is a rare condition and that there is no generally accepted preferred treatment regimen after both ASCT and brentuximab vedotin have failed. The sponsor has also indicated that, due to the rarity of the condition, no Phase III confirmatory study will be performed although the evaluator notes that the accelerated approval for this indication granted by the FDA has the requirement of a randomised Phase III clinical trial in classical Hodgkin lymphoma that '*verifies and isolates the clinical benefit of nivolumab for patients with classical Hodgkin lymphoma*'.

The primary endpoint in the studies presented was objective response rate (ORR). The TGA adopted EMA 'Guideline on the evaluation of anticancer medicinal products in man' does not discuss exploratory studies used as 'pivotal studies' and does not discuss ORR as a suitable end-point. The guideline recommends randomised Phase III studies using the end-points of cure rate, OS and PFS/DFS. Overall survival is the preferred end-point given that end-points such as ORR and PFS/DS may not translate into longer life. However, the guideline does acknowledge that it may not be possible to recruit a sufficiently large number of patients to conduct reasonably powered, randomised studies in '*some truly rare tumours or very narrow indications'.*

Without randomised trials using appropriate comparators, it is difficult to assess the clinical relevance of the reported ORR, particularly when this must be assessed in conjunction with a median duration of response that has been established in only 15 patients (ASCT-Bren Failed group, Study CA209039). The ORR of 60% reported in both studies is clinically meaningful and the median duration of response of 12 months reported for the ASCT-Bren Failed group is several months longer than that reported with other treatment options for this patient group. PFS and OS were secondary end-points in both of the studies, but these results were not

maturing at the time of the interim analysis. However, it is encouraging that the median OS was not reached with median follow-up of 23 months in the ASCT-Bren Failed group.

The TGA adopted EMA 'Guideline on the evaluation of anticancer medicinal products in man' discourages the use historical controls except for circumstances in which '*dramatic effects*' are documented:

'Dramatic effects are uncommonly documented in the treatment of malignancies, but it is acknowledged that such effects, obvious to any qualified observer, are seen occasionally. In these cases, prospective confirmation in randomized, reference-controlled studies is not only unacceptable to investigators, patients and ethics committees, but also unnecessary.'

It is not clear to the evaluator that the biological activity demonstrated by nivolumab in the proposed population meets these criteria.

The evidence provided for nivolumab may also be compared to that provided for brentuximab vedotin for a similar indication. The pivotal study for brentuximab vedotin as salvage therapy in patients with CD30 HL who had relapsed following ASCT was also an early phase study. This open label, single arm study of 102 patients reported an ORR was 75%, with a CR rate of 40%, after median follow-up of 9 months. At that time, estimated median duration of response per IRF for all patients was 6.7 months (95% CI 3.6, 14.8) and not reached for patients with CR; estimated median PFS was 5.6 months and estimated mean duration of overall survival was 27 months. With longer term follow-up (3 and 5 years) reported after regulatory approval, the study found that most progression events occurred within the first 12 months and in patients with partial response; the median duration of response in patients with complete response was 20.5 months; the estimated PFS for all patients was 9.3 months; the estimated median OS for all patients was 40.5 months (not yet reached for patients with CR); the estimated 5-year survival for all patients was 41%. The pivotal study in the submission to the TGA was supported by 2 Phase I studies in which patients with relapsed CD30+ HL who had failed systemic chemotherapy or salvage therapy were treated with brentuximab vedotin at different doses.[31] These studies reported ORRs of 40% and 53%, with CR rate of 26% in both studies.

In comparison to the brentuximab vedotin registrational study, the nivolumab Phase II study has fewer patients but has a similar median follow-up. The nivolumab study found a lower ORR and much lower CR rate; the estimated duration of response was unstable at the time of analysis due to the number of censored patients; the estimated PFS and OS were also immature.

Nivolumab may offer another treatment option for patients with relapsed cHL following ASCT and brentuximab vedotin, however, there are many uncertainties that limit the assessment of benefit. Provision of updated efficacy results for Cohort B of the Phase II study could help resolve these uncertainties.

9.2. First round assessment of risks

Table 79. First round assessment of risks

Risks	Strengths and Uncertainties
Patients with cHL who have failed ASCT followed by brentuximab vedotin treated with nivolumab monotherapy for Cohort B of Study CA209205: · Adverse reactions, all cause, all grades reported in almost all patients (> 98%). Most common reactions: fatigue 36%, pyrexia 31%, cough 27.5%,	Strengths: · Despite the frequency of AEs, there was no apparent effect on average measures of QoL during Weeks 9 to 33 of treatment.

[31] Australian Public Assessment Report (AusPAR) for brentuximab vedotin. Therapeutic Goods Administration; Canberra, Australia. May 2014.

Risks	Strengths and Uncertainties
diarrhoea 27.5%, nausea 24%. · Adverse reactions, all cause, Grade 3 or 4 in 40%. Most common reactions, apart from laboratory abnormalities, were dyspnoea (2.5%), lung infection (2.5%), and rash (2.5%). · SAEs, all cause, reported in 25%, with Grade 3 or 4 in 12.5%. Grade 3 or 4 SAEs were all reported in single patients and included: pneumonia, lung infection, dyspnoea, meningitis, pyrexia, generalised oedema, arrhythmia, pericardial effusion, cardiac failure, gastrointestinal stromal tumour, hypercalcaemia, syncope, rash, maculopapular rash, platelet count decreased, osteonecrosis, febrile neutropaenia and embolism. · Discontinuations due to AEs in 3 patients (3.8%). · Deaths due to nivolumab toxicity reported in one patient (MSOF) (1.25%) although this was changed after database lock. In other cHL patients (Cohort A + C of Studies CA209205 and CA209039), all cause/all grade AEs had a similar pattern although there were higher reporting rates in Study CA209039. There was one other death attributed to nivolumab toxicity, MSOF following PJP. Possible increase in GVHD and other complications in patients having allo-SCT after nivolumab treatment. The immune mediated events of pneumonitis, toxic epidermal necrolysis, Stevens Johnson syndrome, hepatitis, encephalitis, myasthenia gravis, myositis, myocarditis and rhabdomyolysis have each been associated with fatal outcome in patients receiving nivolumab monotherapy.	· Deaths and discontinuations due to nivolumab toxicity were rare. Uncertainties: · Reliability of results given small patient number and noting differences in reported AEs, Grade 3 or 4 AEs and SAEs between the two studies presented by the sponsor. · Generalisability to target population, noting that patients with ECOG > 1 and patients with interstitial lung disease were excluded. · Generalisability from safety as established in patients with solid tumours to patients with cHL, noting increased duration of treatment and different PK in patients with cHL. · Generalisability to wider population given that immune mediated adverse reactions in some patients in the clinical trials had delayed recognition and management despite training and the investigator's brochure.

Without randomised trials using appropriate comparators, it is difficult to assess the clinical significance of the safety of nivolumab in the cHL population. It is also difficult to assess the impact of AEs on patients on the basis of the grade of the AE. The sponsor has provided a differently structured analysis of SAEs for the pooled population that has received nivolumab monotherapy in clinical studies. This found that SAEs were reported in 41.7% of patients, that this resulted in hospitalisation in 36.9% of patients and had fatal outcome in 8.7%. In another 1.5%, the SAE was 'life-threatening'.

Immune mediated adverse reactions are a major concern with nivolumab. These represent a new type of adverse drug reaction and are notable for their non-specific presentations with a high degree of vigilance and pro-active monitoring required for their detection. Early detection and management by dose delay ± immunosuppressive treatment is believed to improve outcome. Immune related AEs are described according to the categories of Endocrine, Gastrointestinal, Hepatic, Pulmonary, Renal, Skin and Other. The 'Other' category now includes: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, hypopituitarism, myasthenic syndrome, encephalitis, myositis, myocarditis and rhabdomyolysis. The additional immune related ARs of gastritis, sarcoidosis, and duodenitis are described with nivolumab + ipilimumab combination therapy. Of note is that the events of pneumonitis, toxic epidermal necrolysis, Stevens Johnson syndrome, hepatitis, encephalitis, myasthenia gravis, myositis, myocarditis and rhabdomyolysis

have each been associated with fatal outcome. Comparison of the reported rates in the different cohorts of Studies CA209205 and CA209039 shows that the most commonly reported categories of endocrine, gastrointestinal and skin appear to increase with the duration of nivolumab treatment. The estimated incidence of Grade 3 or 4 events in each of the categories for the population exposed to nivolumab monotherapy as provided in the most recent PBRER is less than 2%; the estimated incidence of the rarer more serious events such as pancreatitis, encephalitis, myasthenic syndrome, TEN, SJS, GBS, myocarditis, myositis is less than 1%. However, the increasing recognition of a wider variety of AEs with possible immune-mediated cause over the past few years suggests that the safety of nivolumab has yet to be fully characterised. It also suggests that immune related AEs were under-recognised in earlier studies, with illnesses and deaths potentially attributed to progressive disease or other causes, such as infection, rather than immune-mediated conditions. Review of the narratives provided in the interim CSRs in this submission suggests that this may have been the case in some patients.

The narratives provided by the sponsor also indicate that even in the closely monitored setting of the clinical study and with an Investigator's brochure to provide assistance, there were patients in whom an immune-mediated condition did not appear to be considered, with delayed commencement of immunosuppressive treatment and worse outcome. There also appeared to be some haphazard administration of corticosteroids for these conditions. These factors raise considerable concerns regarding the safety that may be achieved outside clinical trials.

A new safety concern has been raised in the cHL population with the possibility of an increase in GVHD and other complications of allo-SCT in patients undergoing this treatment following nivolumab therapy. This is a significant concern as allo-SCT is the only treatment option for patients who relapse after autologous SCT that may have a curative effect.

9.3. First round assessment of benefit-risk balance

9.3.1. Benefit

The main benefit offered by nivolumab in the treatment of patients with relapsed cHL (after ASCT and brentuximab vedotin) is an objective response rate of 60%. Due to the immaturity of the analysis, it is unknown as to whether this will translate into more meaningful outcome measures such as an increase in PFS or OS.

The evaluator notes that nivolumab has received accelerated approval for the proposed indication in the US. However, there is currently no framework for granting conditional/provisional/accelerated approval of drugs by the TGA.

9.3.2. Risk

The main risk is that the reported ORR will not translate into improved PFS or OS. If this is the case, then there will be no benefit and only the risk of AEs due to nivolumab in patients with cHL.

The sponsor proposes that nivolumab be continued until disease progression or unacceptable toxicity. Only the patients in Study CA209039 completed the course of treatment defined in this way; only 3/23 patients were still on treatment after median follow-up of 23 months. At the time of the interim analysis, with median follow-up of 9 months, 51/80 patients in Cohort B of Study CA209205 were still receiving treatment. Comparison of the rates of AEs across the two cHL studies and within the cohorts of Study CA209205 has shown that these rates increase substantially as the duration of treatment increases. Determining a safety profile that can be generalised to the proposed target population requires more mature safety results in a larger group of patients than has been provided by the sponsor. These concerns may be resolved by the provision of updated safety information from Study CA209205.

The benefit-risk balance of nivolumab, given the proposed usage, is undeterminable at this time.

10. First round recommendation regarding authorisation

This evaluator is unable to make a recommendation at this time.

10.1. Issues

10.1.1. Efficacy

The evidence provided by the sponsor is of early analyses of two early phase studies (of 15 and 80 patients respectively), with immature results for the meaningful outcome measures of PFS and OS. The end-point of a consistent ORR of 60% across the two studies is encouraging but the very low CR rate is concerning.

The evaluator has also expressed concern regarding study conduct at two sites, on the basis of disproportionate numbers of relevant and significant protocol deviations and disproportionate reporting of the AE of infusion related reactions.

The evaluator notes that nivolumab has received accelerated approval for the proposed indication in the US. However, there is currently no framework for granting conditional/provisional/accelerated approval of drugs by the TGA.

The evaluator requests updated data regarding efficacy of nivolumab in Cohort B of Study CA209205 and a more comprehensive discussion of the clinical relevance of this to assist in determining efficacy. The evaluator also has a number of other questions regarding efficacy, the sponsor's responses to these questions will further assist in the assessment of efficacy.

10.1.2. Safety

The analysis of safety presented by the sponsor is problematic as it includes patients recently enrolled into other cohorts of Study CA209205 and who have received few nivolumab treatments. However, within the limitations of the patient numbers and varying durations of therapy, nivolumab treatment appears to be well tolerated although there were 2 deaths attributed to nivolumab toxicity (in 263 cHL patients).

However, there is uncertainty regarding the rate of AEs/SAEs with longer duration therapy, the reported rates were higher in the ASCT-Bren Failed group of patients, almost all of whom had discontinued treatment after a median follow-up of 23 months. At the time of the interim analysis of Cohort B, the median duration of follow-up was 9 months with 64% of patients were continuing on treatment. More mature safety results from Cohort B would enable determining the rate of AEs/SAEs with longer durations of therapy.

There is also uncertainty regarding whether the safety of nivolumab monotherapy is comparable to that reported with other tumour types. The duration of nivolumab treatment appears to be considerably longer in patients with cHL (on the basis of the median number of doses) and some data suggests higher rates of Grade 3 or 4 AEs and SAEs in the cHL group. Also of note is the apparently different PK of nivolumab in patients with cHL, with decreased clearance resulting in a longer half-life and increased exposure (according to C_{avgss}). Patients with cHL may experience a higher rate of AEs/SAEs due to both longer duration of treatment and progressively increasing serum concentration.

Immune mediated adverse reactions are a major concern with nivolumab. These represent a new type of adverse drug reaction and are notable for their non-specific presentations with a high degree of vigilance and pro-active monitoring required for their detection. Early detection and management by dose delay ± immunosuppressive treatment is believed to improve outcome. The narratives provided by the sponsor indicate that even in the closely monitored setting of the clinical study and with an Investigator's brochure to provide assistance, there were patients in whom an immune-mediated condition did not appear to be considered, with delayed commencement of immunosuppressive treatment and possible worse outcome. There

also appeared to be some haphazard administration of corticosteroids for these conditions. This raises considerable concerns regarding the safety that may be achieved outside clinical trials.

The evaluator requests updated data regarding safety of nivolumab in Cohort B of Study CA209205, and Cohorts A and C, together with an updated comparison to other tumour types to assist in determining safety of nivolumab for the proposed usage. The evaluator also has a number of other questions regarding safety and the sponsor's responses to these questions will further assist in the assessment of safety.

11. Second round evaluation of clinical data submitted in response to clinical questions

11.1. Background

11.1.1. Question 1: Wording of the indication

Three different versions of the wording of the proposed indication are provided in the sponsor's documents, with the differences indicated in red text below.

1. In the cover letter for the dossier:

   'Opdivo, as monotherapy is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) following after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin,

   or

   after following at least two prior therapies in patients who are not candidates for ASCT'.

2. In the Pre-planning form:

   'Opdivo, as monotherapy is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) following autologous stem cell transplant (ASCT) and brentuximab vedotin

   or

   following at least two prior therapies in patients who are not candidates for ASCT'.

3. In the proposed PI:

   'Opdivo, as monotherapy is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin,

   or

   after at least two prior therapies in patients who are not candidates for ASCT'.

4. In the Clinical Overview:

   '[The sponsor] is seeking an indication for nivolumab as monotherapy for the treatment of adult patients with cHL who have received:

   ASCT and treatment with brentuximab vedotin, or

   after at least 2 prior therapies in patients who are not candidates for ASCT.'

Could the sponsor please clarify the wording for the proposed indication?

11.1.1.1. Sponsor's response

The sponsor clarified the wording that was proposed at the time of the submission. This has however, been superceded by the sponsor's amendments to the proposed wording in response to the Questions 4, 38, and 39.

11.1.1.2. Evaluator's response

The amended indication statement and further revisions to the indication are discussed in Questions 4, 38 and 39.

11.1.2. Question 2: Confirmatory Phase III study

The sponsor has indicated, in email correspondence and in the cover letter for this submission, that there is no intention to perform a confirmatory Phase III study. The reasons given were that: '*The available evidence for submission supports a very narrow indication for which it was not possible to recruit a sufficiently large number of patients to conduct a reasonably powered, randomised Phase III study. As a consequence, the sponsor has not conducted nor is planning a confirmatory Phase III study in this precise patient population due to the small number of patients available, the late stage of disease and the absence of an approved comparator.*'

The sponsor's cover letter provides the following additional information: '*[The sponsor] is however planning a Phase III trial in an earlier treatment line in patients with cHL. Study design options are still being investigated.*'

Post market requirements of the FDA included a randomised Phase III study in cHL that '*verifies and isolates the clinical benefit of nivolumab for patients with cHL*', and that has PFS by IRRC as the primary endpoint, and OS as a secondary endpoint.

Table 80. FDA post market requirements and commitments

Requirement/Commitment Number: 1

Required Under:	Accelerated Approval
Original Projected Completion Date:	12/31/2026
Description:	Conduct a randomized phase 3 clinical trial in classical Hodgkin lymphoma that verifies and isolates the clinical benefit of nivolumab for patients with classical Hodgkin lymphoma. The primary endpoint would be progression-free survival as determined by an independent review committee. Overall survival would be a key secondary endpoint.
Current Status:	Pending

Requirement/Commitment Number: 2

Required Under:	FDAAA Section 505(o)(3)
Original Projected Completion Date:	12/31/2022
Description:	Characterize complications after allogeneic hematopoietic stem cell transplantation (HSCT) following nivolumab in at least 90 patients with classical Hodgkin lymphoma, of which at least 50% had received nivolumab alone or in combination as the regimen immediately prior to the allogeneic HSCT conditioning regimen. Evaluate toxicities at least through transplant Day 180, and include details of prior nivolumab treatment and the transplant regimen. Characterize toxicities including hyperacute graft-versus-host disease (GVHD), severe (grade III-IV) acute GVHD, febrile syndromes treated with steroids, immune mediated adverse events, pulmonary complications, hepatic veno-occlusive disease, critical illness, and transplant-related mortality. Toxicities may be characterized prospectively, or through a combination of prospective and retrospective data analysis.
Current Status:	Pending

Could the sponsor provide more information regarding the planned Phase III study referred to in the cover letter and any planned Phase III study that will be used to meet the FDA's post-market requirement?

11.1.2.1. Sponsor's response

The sponsor's response is that a randomised, Phase III, open-label trial of single agent brentuximab vedotin (BV) versus BV and nivolumab in patients with relapsed and/or refractory Hodgkin Lymphoma (HL) will be conducted. This decision was apparently based on the

preliminary efficacy observed in ongoing trials with the combination of nivolumab and BV. Two early-phase ongoing studies of the nivolumab and BV combination were described:

- A Phase I/II study of up to 4 cycles of the combination of brentuximab vedotin (bv) and nivolumab for relapsed or refractory Hodgkin lymphoma in adults after failure of standard first-line chemotherapy (ClinicalTrials.gov identifier: NCT02572167). Preliminary results for 20 patients who had received 4 cycles of the combination regimen were an objective response rate (ORR) of 90% and complete metabolic response (CMR) of 62%.
- the ECOG ACRIN trial E4412, a Phase I study with an expansion cohort of the combinations of ipilimumab, nivolumab and brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma (ClinicalTrials.gov identifier: NCT01896999) in 10 patients with relapsed/refractory disease. The preliminary data from the E4412 trial with a sample size of N = 10 for relapsed/refractory patients has demonstrated an ORR of 100% and complete response (CR) of 63%.

A description of the planned Phase III study was provided:

- The patient population will include relapsed refractory classical Hodgkin lymphoma (cHL), after failure of ASCT or patients who are ineligible for ASCT. Prior pre-treatment with brentuximab vedotin was allowed provided that disease progression had not occurred on BV or BV had not been discontinued due to AEs.
- The primary endpoint for the trial is to compare the complete response rate (CRR)/CMR of the combination brentuximab vedotin and nivolumab with single agent brentuximab vedotin with a minimum follow up of 6 months. The co-primary endpoint is to compare progression free survival (PFS) of the combination brentuximab vedotin and nivolumab with single agent brentuximab vedotin.
- Approximately 360 participants are planned to be screened, such that approximately 300 participants will be randomised to receive either nivolumab/brentuximab vedotin or brentuximab vedotin in a 1:1 ratio.

11.1.2.2. Evaluator's response

The sponsor has confirmed that there will be no confirmatory study for either part of the proposed indication. The open label Phase III study described in the sponsor's response has two arms: brentuximab vedotin versus brentuximab vedotin + nivolumab and will not be investigating nivolumab monotherapy in the relapsed/refractory cHL population. According to the sponsor's response, the planned Phase III study will be the 'the Phase III registration trial' as it will be conducted in relapsed refractory HL. In the absence of an arm that has nivolumab as a single agent, none of these studies can provide any additional information to support the indication that is the subject of this submission.

The final analysis of Cohort A and Cohort C of Study CA209205 will provide some information regarding the efficacy of nivolumab as monotherapy in patients with relapsed/refractory cHL. Cohort A was to include patients who have received ASCT but not brentuximab vedotin and Cohort C was to included patients who have received ASCT and brentuximab vedotin but not in any specific order. The evaluator notes that in the response to Question 20, the sponsor stated: '*A subsequent DBL for all 3 cohorts took place on 28 June 2016 after requisite minimum follow-ups for Cohorts A (9 months) was met*'. This suggests another protocol amendment in the timing of analyses as the study protocol provided in the sponsor's submission specified a minimum duration of follow-up of 12 months for Cohort A and C (as did an earlier protocol for Cohort B). It is important that the CSR with efficacy results for Cohorts A and C is provided to the TGA when available.

Neither the planned 'Phase III registrational study' nor the efficacy results for Cohorts A and C of Study CA209205 will be able to provide any evidence to support the use of nivolumab monotherapy in patients who are ineligible for ASCT. As there was very little information to support this part of the indication in the dossier and given that there will be no further

information from planned studies, the evaluator is of the opinion that the indication will require further revision.

11.1.3. Question 3: EMA reports and request for supplementary information

From the sponsor's documentation, an extension of indication submission for the indication of:

> *'Opdivo as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL):*
>
> *after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin,*
>
> *or*
>
> *after at least two prior therapies in patients who are not candidates for ASCT'.*

This was made to the EMA in March 2016. This extension of indication was discussed at the 20 June to 23 June 2016 CHMP meeting.[32] According to the publically available minutes of the meeting:

'The Committee discussed the issues identified in this application. The main focus of the discussion related to the efficacy data and the wording of the indication. Particularly for patients who are not considered for autologous stem cell transplant further data was required to a thorough assessment. The Committee adopted a request for supplementary information with a specific timetable.'

The CHMP subsequently gave a positive recommendation for the cHL indication, although with revised wording.

The sponsor is requested to provide any updated reports or supplementary information provided to the EMA that has not been provided to the TGA and to provide the final CHMP report.

11.1.3.1. Sponsor's response

According to the sponsor's response, the application to the EMA was submitted in March 2016. The CHMP raised concerns regarding:

- the broadly claimed indication with limited data, particularly in the ASCT-naive population with at least 2 prior therapies
- cases of acute GvHD observed after allo-SCT in cHL patients treated with nivolumab and requested the Sponsor provide an update of the safety of the next line treatments for cHL after nivolumab with special attention to GvHD.

In the sponsor's response to these concerns, a revised indication was proposed:

> *'Opdivo as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin'.*

Updated results were also provided, with an update on efficacy for the Phase II Study CA209205 (per the 19 April 2016 database lock; 14 June 2016 for IRRC database lock); updated safety from a database lock of 9 February 2016 for Study CA209205 and 8 February 2016 for Study CA209039. A brief summary of the efficacy results as provided to the EMA was provided in the sponsor's response and it was noted that '*Patient characteristics, transplant details, and post-allogeneic HSCT safety information were additionally summarized to address the CHMP concerns on cases of acute GvHD observed after allo-SCT in cHL patients treated with nivolumab*.'

According to the sponsor's response, *'the sponsor received the EC Adoption of the Commission Implementation Decision taken on 21 November 2016, to extend the Opdivo indication to include*

[32] CHMP Minutes for the meeting on 20 June to 23 June 2016.

treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.'

11.1.3.2. Evaluator's response

The full response as provided to the CHMP was not included in the sponsor's response; a draft EPAR was not provided. From the EMA website, the extension of indication was recommended by the CHMP on 13 October with the wording as shown above. On 12 January 2017, the indication for cHL was listed in the approved indications for nivolumab on the EMA website with the wording:

> *'Opdivo is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.'*

An updated SmPC was also listed on the website on that date. The EPAR was not available (last checked 16 January 2017).

The evaluator notes that both the EMA and the FDA have rejected the second part of the proposed indication in its entirety, that is, use in patients who are not eligible for ASCT was not approved.

The evaluator also notes that in response to a request for updated efficacy data (see Question 16, below) the sponsor has provided an analysis with the 19 April 2016 database lock for Study CA209205 that is the same as that provided to the EMA several months earlier.

11.1.4. Question 4: Note to the indication

In the dossier, Details of Compliance with Pre-submission Meeting Outcomes, the following written advice provided to the sponsor by the TGA delegate is documented:

'Any reliance on early data where there are immature or surrogate endpoints would need to be communicated prominently and clearly in the PI, and for such applications, the TGA has been requiring a Note to the Indication and a statement in the Clinical Trials section.'

Given that there is a reliance on both early data and surrogate end-points for the demonstration of efficacy, can the sponsor please comment on why the requested Note to the Indication has not been included? See also Question 39: Wording of the indication in the PI, below.

11.1.4.1. Sponsor's response

The sponsor has included a Note to the Indication.

11.1.4.2. Evaluator's response

The wording of the Note to Indication, as proposed by the sponsor and as preferred by the evaluator, is discussed in Question 39: Wording of the indication in the PI, below.

11.2. Pharmacokinetics

11.2.1. Question 5: Full PK profile schedule and analyses in Study CA209039

According to the Study CA209039 protocol, 5 patients in each of the tumour cohorts will follow the full PK profile schedule and the remaining patients in the tumour cohorts will follow the sparse sampling schedule. No information was provided regarding the PK results of these 5 patients could be located by the evaluator in the CSR. Was this component of the study performed? If yes, did it confirm the decreased clearance seen in the PPK analysis?

The protocol for Study CA209039 (Appendix 1.1 of the CSR) also states that the pharmacokinetic analyses were to be: *'Summary statistics will be tabulated for the pharmacokinetics parameters of nivolumab by dose and study week, as appropriate. To describe the dependency on dose, scatter plots of nivolumab C_{max} and $AUC_{(0-T)}$ versus dose will be provided for each day measured. To assess attainment of steady state, plots of C_{min} versus time will be*

provided.' These analyses have not been provided in the interim CSR. The pharmacokinetics of nivolumab appears to be different in patients with cHL compared to patients with solid tumours (according to the PPK analysis). This makes the source data of great importance. Could these analyses please be provided?

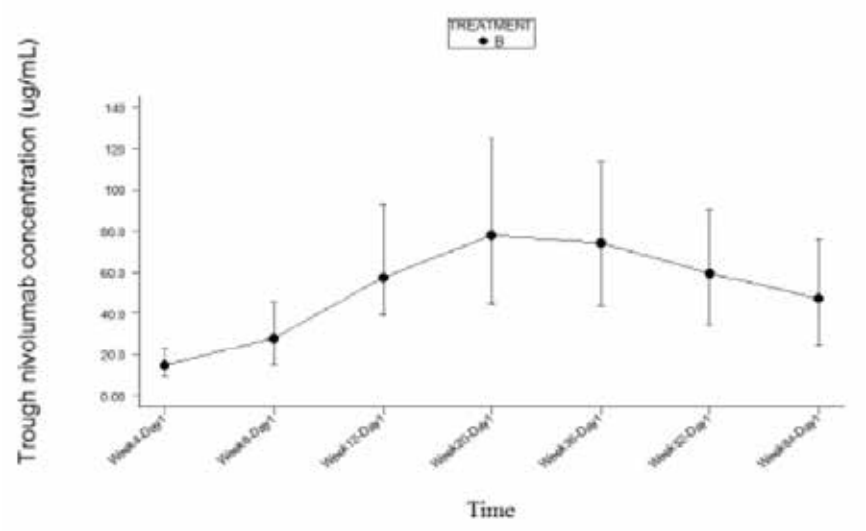
11.2.1.1. Sponsor's response

According to the sponsor's response, there were 18/23 cHL subjects in Study CA209039 who received nivolumab 3 mg/kg monotherapy and had intensive PK sample collection for up to 21 days (504 hours) after first dose, with sparse sampling thereafter. The PK parameters of nivolumab, including T_{max}, C_{max}, $AUC_{(0-336)}$, and $AUC_{(0-504)}$, for these 18 cHL subjects are shown in Table 81 and Figure 25 below. CL could not be derived due to the short collection time relative to the nivolumab half-life. Geometric mean trough concentrations of nivolumab over time are shown in the figure below. According to this plot, steady-state nivolumab exposure was not achieved by Week 12 in cHL subjects. The observed steady state exposures of nivolumab ($C_{min,ss}$, geometric mean: 78 µg/mL, CV: 32.7%) in Study CA209039 are consistent with the $C_{min,ss}$ (geometric mean: 92.8 µg/mL, CV: 28.5%) estimated by the PPK model and were greater than estimated $C_{min,ss}$ in solid tumours (geometric mean: 57.3 µg/mL, CV: 42.4%).

Table 81. Summary statistics for PK parameters of nivolumab after first 3 mg/kg dose (Study CA209039)

Tmax (h) Median [n] (Min-Max)	Cmax (µg/mL) Geo.Mean [N] (%CV)	AUC(0-336) (µg•h/mL) Geo.Mean [N] (%CV)	AUC(0-504) (µg•h/mL) Geo.Mean [N] (%CV)
1.1 [18] (1, 4.07)	55.7 [18] (22.8)	9138.9 [18] (27.1)	11848.0 [17] (28.5)

Figure 25. Nivolumab trough concentration (geometric mean (95% CI)) over time (Study CA209039



The sponsor concluded that, overall, the results obtained from non-compartmental analysis of nivolumab in cHL patients are consistent with that of the PPK analysis which found that the half-life of nivolumab in cHL patients (40 days) was greater than that in solid tumors (26 days). In addition, nivolumab exposures and time to steady state in cHL patients were greater than those seen in solid tumours, indicating decreased CL of nivolumab in cHL patients.

11.2.1.2. Evaluator's response

According to the response to Question 11 (below), intensive sampling was performed for the first dose of nivolumab in Study CA209039, although only for 21 days after the first dose. The results of the analysis of sampling of trough concentrations in subsequent samples, with steady state not achieved until 20 weeks, provides useful support to the findings of the PPK analysis of

altered PK in patients with cHL compared to patients with solid tumours, also of note are the CV% of < 30% for the geometric mean values of the parameters shown. This inter-individual variability is consistent with that seen in patients with solid tumours as is further demonstrated by the sponsor in the response to Question 11 (below).

11.2.2. Question 6: The PPK analysis and number of patients from Study CA209205

According to 2 tables of the PPK report [not included here], the PPK analysis included 170/239 patients from Study CA209205, with 36 patients from Study CA209205 excluded due to having pre-treatment specimens only. The sponsor was requested to advise of the reason(s) for the other 33 patients from Study CA209205 not being included in the analysis.

11.2.2.1. Sponsor's response

According to the sponsor's response, the PK lock date (31 July 2015) occurred before the Oracle Clinical (OC) lock date (2 October 2015). These samples from these subjects were either collected after the PK lock date, or shipped after the sample shipment cut-off date. It should be noted that the study is ongoing and collection of PK data is continuing.

11.2.2.2. Evaluator's response

This is acceptable

11.2.3. Question 7: The PPK analysis and the number of samples from Study CA209039

According to a table [not included here] of the PPK report, there were 224 samples from the 23 patients in Study CA209039 included in the PPK analysis, an average of 9 samples per patient. However, this is not consistent with the information provided in an appendix of the CSR for Study CA209039. According to the CSR, this appendix *'provides a by-subject listing of nivolumab concentrations along with corresponding immunogenicity*'. This appendix has only 99 serum nivolumab results (not including baseline samples). Can the sponsor please account for this discrepancy?

11.2.3.1. Sponsor's response

[This] appendix of the Study CA204039 CSR is a table that serves as a listing of ADA sampling results. The corresponding PK sampling results were also provided in this table in order to demonstrate that nivolumab concentration did not interfere with the ADA detection. As shown in a table [not included here] of the Study CA209039 protocol, blood samples for ADA assessment were not collected at every PK sampling time point. Specifically, during the first cycle of nivolumab treatment, seven PK samples were collected from Day 1 to Day 22, while ADA samples were only collected at two pre-dose time points (Day 1 and Day 22). Additionally, ADA samples were not collected at the End of Infusion (EOI) time point at Week 12, while PK samples were collected at that time point. Among the 224 PK samples, 112 of them did not have corresponding ADA samples because of the abovementioned reasons. There were 13 PK samples that did not have corresponding ADA assessment available either due to ADA samples not analysed or due to samples not shipped at the time of data cut-off. Thus, this appendix is not meant to represent an exhaustive list of PK samples, it is mainly a by-subject listing of nivolumab ADA with corresponding PK.

11.2.3.2. Evaluator's response

The data provided in the appendix in the CSRs for Studies CA209039 and CA209205 has been a source of some confusion for the evaluator, with this resulting from the wording used in the CSRs. The link provided in the Pharmacokinetics Results section of the CSR for Study CA209039 was *'[The] appendix provides a by-subject listing of nivolumab concentrations along with corresponding immunogenicity*'. A link with similar wording was provided in the same section of the CSR for Study Ca209205. This was interpreted by the evaluator as meaning that the primary intent of these tables was to provide the pharmacokinetic data rather than to provide ADA data.

Following the clarification provided above, the evaluator accepts that this appendix did not provide results of all of the PK samples that were collected.

11.2.4. Question 8: The PPK analysis and sample distribution for Studies CA209039 and CA209205

The PPK analysis has indicated that patients with cHL have a lower clearance of nivolumab in comparison to patients with solid tumours. The evaluator is concerned that this may be an unreliable finding due to small sample numbers and limited sampling per patient in the cHL population.

According to the PPK report, there were 224 samples from 23 patients in Study CA209039 included in the analysis (although this is not consistent with the CSR for Study CA209039; see Question 7 above) and 344 samples from 170 patients included from StudyCA209205.

From the by-subject listings provided in the Study CA209039 only 15 patients had regular nivolumab concentrations reported for time-points during the first 4 to 6 months; in Study CA209205 only 39 patients had a sequence of 4 serum concentration measurements available.

Using figures in the PPK report [not included here] as examples, could the sponsor provide frequency distributions of these samples from patients in StudiesCA209039 and CA209205 with:

1. Number of samples per patient
2. Number of samples according to time since previous dose

Could the sponsor also indicate the number and proportion of samples for both the cHL population and the overall population that were from repeated dosing? This could be shown as a frequency distribution of the number of samples per patient.

11.2.4.1. Sponsor's response

The requested plots are provided below in Figures A to D.

In cHL population, 39% subjects had 3 or more samples; 74% of samples were collected between day 10 and day 20 after previous dose. After repeated dosing (number of doses ≥ 2), 39% subjects (N = 192) in cHL population had 3 or more PK samples, which is similar to the proportion in the overall population (45%, N = 1466). As explained in the response to Question 9 (below) the effect of cHL tumour type was adequately estimated with the submitted data. The subsequent comprehensive PPK analysis with more data from more subjects confirmed the submitted analysis and is shown below in Figures 26 to 29.

Figure 26. Distribution of number of PK samples per subject for cHL population (Studies CA209039 and CA209205)

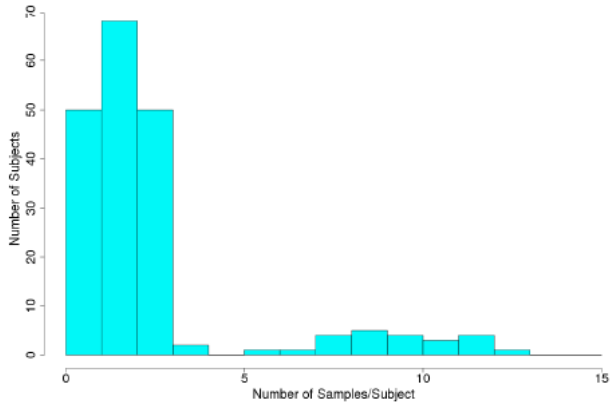


Figure 27. Distribution of number of PK samples at actual time after previous dose for cHL population (Studies CA209039 and CA209205)

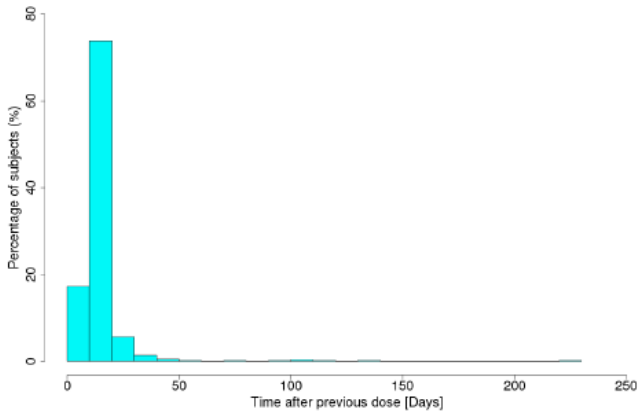


Figure 28. Distribution of number of PK samples per subject for cHL population after repeated dosing (Studies CA209039 and CA209205)

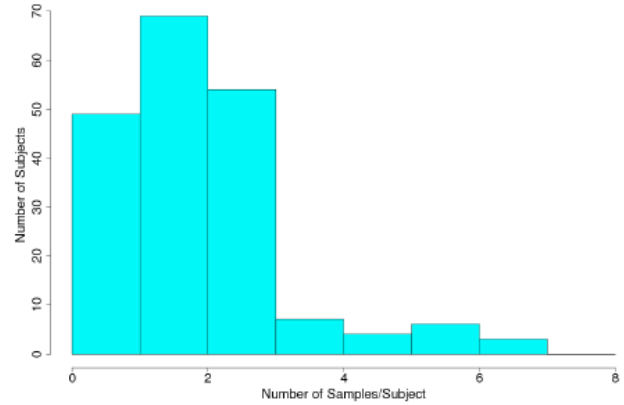
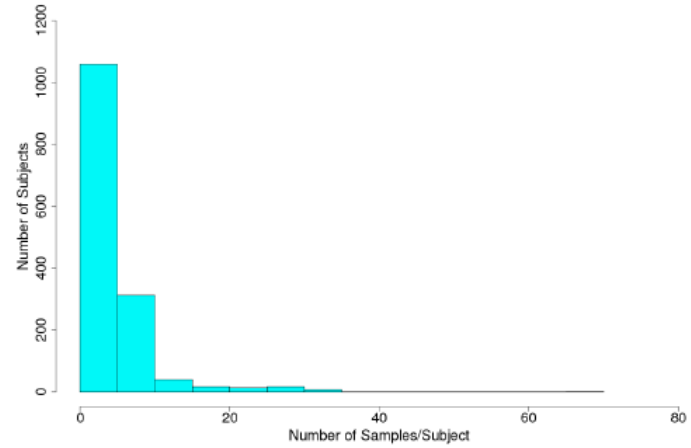


Figure 29. Distribution of number of PK samples per subject for overall population after repeated dosing



11.2.4.2. Evaluator's response

The evaluator notes the responses to earlier questions that indicated that the evaluator had misinterpreted the appendix in each CSR as containing all of the PK results performed during the study (to database lock). The response to this question (and others) by the sponsor shows that, although there were more results, there were still very few patients in whom > 3 samples were collected and 18 instead of 15 patients in whom sampling was performed over several months. The sponsor has commented that the 'proportion' of patients in whom 3 or more samples were collected was similar in the cHL group to other tumour types; the evaluator notes

that the actual patient number in the cHL group who had sampling after repeated dosing is very small compared to the number of patients with solid tumours (15 compared to 660 patients).

11.2.5. Question 9: Reliability of the PPK finding of reduced clearance and drug accumulation in Studies CA209039 and CA209205

The evaluator is concerned that the apparent difference in clearance of nivolumab by patients with cHL may be a product of the limited number of patients, limited sampling and inter-patient variability: in Study CA209039 only 15 patients had regular nivolumab concentrations reported for time-points during the first 4 to 6 months; in Study CA209205 only 39 patients had a sequence of 4 serum concentration measurements available. Could the sponsor please comment?

11.2.5.1. Sponsor's response

The sponsor's response listed the number of subjects and samples that were included in the PPK analysis: 193 subjects with cHL provided a total of 568 samples; 19 subjects in Study CA209039 and 61 subjects in Study CA209205 had PK samples at or longer than 120 days following initiation of nivolumab treatment. The response stated that the effect of cHL tumour type on nivolumab CL was reasonably estimated given the relatively tight 95% CI (62.18, 74.32) of the point estimate (67.98) in the full PPK model.

The sponsor also provided a new PPK analysis where nivolumab PK was characterised across multiple tumour types and a time-varying CL model was used to capture the trend of nivolumab CL decreasing with time. This analysis was reported to include 282 more PK samples from 63 more cHL subjects from CA209205 and 2 more samples from CA209039. The new analysis included 149 subjects that had PK samples collected longer than 120 days and 77 subjects with samples collected for longer than 180 days, up to 392 days.

In the new analyses, time varying effect on CL was described by a sigmoid E_{max} model. Nivolumab CL decreased over time with approximately 26% maximal reduction from baseline values. However, the effect of cHL tumour type on nivolumab CL in this PPK analysis was consistent with that reported in the submitted analysis. That is, nivolumab CL was lower in cHL patients when compared to NSCLC patients. In addition, this effect was adequately estimated with a point estimate (95% CI) of 74.2 (69.5, 78.7) in the full covariate model. The effect of cHL on CL was adequately estimated with a RSE of 8.44% in the final model.

11.2.5.2. Evaluator's response

The new PPK analysis, with the report date of August 2016, was provided as a separate document of 862 pages. The Background section of the report provides some insights. The initial PK analysis was described as a stationary model in which the PK parameters were constant with respect to time. The report then notes that, '*in a subsequent exploratory analysis following guidance from the US FDA, it was found that nivolumab clearance (CL) tended to decrease with time. Therefore, the objectives of this analysis were to re-characterize the PPK of nivolumab across multiple tumor types, using a time varying CL model and perform an assessment of the effect of covariates on nivolumab PK*'. The tumour types investigated in the new analysis included 'UC, GC, SCLC, NSCLC, melanoma, RCC, SCCHN and cHL'. The co-variates investigated were body weight (BBWT), age, sex, race, hepatic function status, eGFR, baseline performance status (PS) and tumour type. The effect of baseline serum albumin, baseline LDH, baseline tumour size and ADA status on nivolumab PK were assessed in sensitivity analyses, as data on the first three factors was not available for all tumour types. A comparison of Japanese to non-Japanese patients was also made.

This new PPK analysis is summarised below. It has not been fully evaluated given the time constraints of a second round evaluation.

A total of 3729 patients from 19 studies were included in the analysis (out of 3811 treated in the studies). Patients in whom no PK samples were available or in whom clinical information were flagged and removed from the analysis. Samples were excluded from the analysis if they

were below the LLQ or if date/time information was missing. In the dataset: 67% were male; 88.6% were white; tumour types were melanoma 25%, lung cancer 25%, renal cell carcinoma 20%, bladder cancer 9%, cHL 7.4% and small numbers of other types; ECOG PS ≥ 2 1.71 %; moderate liver impairment 0.29%.

The final model was developed from the full model with tumour types grouped together by step-wise backward elimination of covariates, based on a combination of p-value cut-off ($p > 0.01$) and Bayesian information criterion (BIC).

According to the report: *'The final model was a two-compartment, zero-order IV infusion and time-varying CL (sigmoidal Emax function) with a proportional residual error model, with random effect on CL, VC, VP and Emax and correlation of random effect between CL and VC.'*

Analyses using the final model found that:

- The model estimated that steady state would be reached at the dose 8 to 9 (16 to 18 weeks) and that approximately 4 fold accumulation according to trough levels would occur before steady state was reached.
- Sex did not result in a difference in exposure.
- In patients with ECOG PS ≥ 2, CL appeared to be higher.
- Nivolumab PK is not affected by mild and moderate renal impairment (eGFR 30 to 90 mL/1.73 m^2) as the increases in exposure were < 10%. A higher exposure was seen in patients with severe renal impairment but this group only included 6 patients.
- Nivolumab CL is not affected by mild hepatic impairment. There were insufficient numbers for any conclusions regarding moderate or severe hepatic impairment (11 patients).
- Nivolumab exposure (dose-normalised $C_{avg,ss}$) was similar across age ranging from 18 to 90 years old, although the numbers of patients aged < 30 years or > 80 years was small.
- Race, baseline LDH and ADA status had no effect on nivolumab CL and exposure.
- Baseline albumin (BALB) affected nivolumab PK such that exposure increased with increasing albumin concentrations: subjects with BALB concentrations of 1.4 g/dL and 5.3 g/dL are expected to have differences in CL of 135% higher and 18% lower, respectively, relative to the subject with 4 g/dL (the reference concentration used in the sensitivity analysis). It was also noted that patients with higher ECOG PS tended to have lower albumin levels (correlation co-efficient -0.35) and the albumin effect may partly represent an ECOG PS effect.
- Over the range of baseline tumour size from 1.0 cm and 65.1 cm CL could be 11% lower and 30% higher, respectively, relative to the subject with a tumour size of 7.7 cm (the reference baseline tumour size used in the sensitivity analysis). Despite this approximation, the effect of tumour size on CL is not considered significant.
- The effect of PDL1 expression (using 5% cut-off) found that CL was similar between positive and negative patients.

With respect to tumour types, the final model found that CL was generally similar across tumour types relative to the reference NSCLC2L+, except for gastric carcinoma and cHL. In cHL subjects, nivolumab CL is lower relative to subjects with NSCLCL2+ (approximately 26%), while subjects with GC exhibit higher CL estimates than the reference NSCLC2L+ (approximately 20%), with corresponding effects on exposure. For subjects with cHL tumour type, exposures were found to be approximately 39% higher relative to the reference NSCLC2L+ and subjects with gastric cancer were found to have exposure approximately 19% lower.

The new PPK analysis includes a greater number of patients and samples (including from patients with cHL) and a different model type. This second PPK analysis confirmed the findings of the first analysis in regard to nivolumab PK in patients with cHL that is nivolumab

demonstrated reduced clearance in patients with cHL compared to patients with solid tumours. The new PPK analysis found that nivolumab PK was also different in patients with gastric cancer and patients with ECOG PS ≥ 2, although clearance was increased in these patients. The report offered no speculation as to how tumour type might affect clearance nor did it propose any different dosing regimen according to tumour type.

11.2.6. Question 10: Reduced clearance and drug accumulation in Studies CA209039 and CA209205

By-subject listing of nivolumab concentrations was provided in the appendices for both of these studies, with sampling occurring pre-dose at different time-points during the treatment and follow-up periods of the studies. For those patients in both studies for whom there was a complete sequence of 3 to 4 post-baseline serum concentration measurements available, there appeared to be a progressive increase in nivolumab concentration over time, suggesting accumulation of nivolumab. The PPK analysis provided also reported that nivolumab clearance was lower in patients with cHL with this resulting in a 43% increase in nivolumab exposure, according to $C_{avg,ss}$. The evaluator notes that this was, according to the PPK report, was the first instance of different CL by tumour type observed in the nivolumab development program decrease in clearance with a specific tumour type.

How does the sponsor account for this difference in clearance, and corresponding increase in exposure, in patients with cHL? Does this have implications for the dosing interval and/or dose in this patient group? The evaluator notes that the sponsor's cited reference in the Summary of Clinical Pharmacology (Li et al) suggests that different doses of rituximab may be appropriate in different patient populations due to the differing clearance.[24]

11.2.6.1. Sponsor's response

Comment: The following response is provided verbatim as it discusses the clinical implications of reduced clearance and dosing.

In the PPK analysis, cHL tumour type was a significant covariate which was associated with a 32% decrease in CL relative to non-small cell lung cancer (NSCLC). While a conclusive reason for lower CL (that is, longer beta half-life in cHL) is unknown, it may be associated with the lower expression of PD-1 in cHL versus solid tumours. It has been reported that tumour-infiltrating T cells from cHL biopsy samples express lower levels of PD-1 compared to corresponding T cells from solid tumours. In solid tumours, the expression of PD-1 is highly associated with the expression of PD-L1. In tumours, such as melanoma, NSCLC, and RCC where PD-L1 expression is high, PD-1 expression is also high. However, in cHL the expressions of PD-1 and PD-L1 do not appear to be associated with each other. Reed–Sternberg (R-S) cells are highly PD-L1 positive, but PD-1 expression in TILs is low. Because the target of nivolumab is PD-1 on T cells, these differences in PD-1 expression between tumour types may have an effect on the PK of nivolumab.

Rituximab, a monoclonal antibody that targets CD20 antigen on B lymphocytes, also demonstrated differing CL among different diseases (chronic lymphocytic leukaemia (CLL) versus non-Hodgkin lymphoma (NHL)) due to altered target cell binding. Because there was significant difference in rituximab exposures between responders and non-responders, increased doses of 500 mg/m2 of rituximab were suggested in CLL patients to attain similar exposures to that achieved with doses of 375 mg/m^2 in NHL patients. However, this is not the case for nivolumab. First, nivolumab exposure-response relationship for efficacy was relatively flat in cHL patients. Second, nivolumab 3 mg/kg doses showed a clinically meaningful response, with an ORR of 65.3% by IRRC assessment. Last and most importantly, the higher exposures of nivolumab 3 mg/kg did not result in a greater risk in cHL patients. Although nivolumab CL in cHL subjects is 32% lower relative to NSCLC subjects, it is not expected to result in any clinically meaningful effect as the exposure-response analyses demonstrated that nivolumab exposure was not a significant predictor of the risk of G3+ DR-AEs. Furthermore, with the safety profile of nivolumab established up to the dose level of 10 mg/kg, 43% greater exposures (C_{avg}) in cHL

subjects relative to solid tumour subjects are still within the range of exposures seen with the 10 mg/kg Q2W dosing regimen (95 percentile of $C_{avg,ss}$: 400 µg/mL) and are not considered clinically meaningful. Additionally, the overall safety profile of nivolumab in cHL was consistent with the overall safety profile of nivolumab in other tumour types. Therefore, based on the abovementioned information, there is no need to modify nivolumab dose or dosing interval for cHL patients.

11.2.6.2. Evaluator's response

The evaluator notes that the new PPK analysis provide in the response to Question 9 (above) found that nivolumab PK were also different in patients with gastric cancer and patients with ECOG PS ≥ 2, although clearance was increased in these patients. The speculation regarding differing expression of PD-1 on tumour infiltrating lymphocytes in cHL compared to other tumour types as a mechanism for reduced clearance is not translatable to these other populations. The evaluator is of the opinion that the pharmacokinetics of nivolumab have not been fully characterised.

The evaluator is also of the opinion that the safety profile of nivolumab in patients with cHL has not been satisfactorily demonstrated to be no worse than that reported in patients with solid tumour types. See also Question 27: Updated comparison across tumour types.

11.2.7. Question 11: Inter-individual variability in serum nivolumab concentrations in Studies CA209039 and CA209205

The by-subject listings of serum nivolumab concentration indicate considerable inter-individual variability, for example in Study CA209205, for patients who had a complete sequence of 4 specimens at Baseline, pre-dose Cycle 3, pre-dose Cycle 7 and pre-dose Cycle 13, inter-individual nivolumab concentrations at similar time-points could vary by 2 to 3-fold. In Study CA209003, the inter-individual variability in PK parameters was considered to be modest with coefficients of variation being < 30% for C_{max} and AUC, after single or multiple dosing. It is not clear to the evaluator as to whether the degree of inter-individual variability in serum nivolumab seen in patients with cHL is consistent with that of patients with solid tumours.

Could the sponsor please comment?

11.2.7.1. Sponsor's response

The sponsor commented that '*it is not appropriate to use trough concentration data to estimate the variability of nivolumab PK parameters as they did not take into account the modulatory effect of different covariates'* and that a PPK analysis provided a more robust estimate of variability because it accounted for the effect of covariates, such as body weight, age, gender, ADA, GFR, albumin, and patient performance status.

In tables [not included here] of the PPK report provided in the dossier, the inter-individual variability for nivolumab exposures derived from estimated PK parameters were not greater than that of solid tumours: the CV% for C_{avgss}, C_{maxss}, and C_{minss} in cHL were 25.8%, 21.9%, and 28.5%, respectively compared to the CV% in solid tumours of 35.4%, 48.7%, and 42.4%, respectively.

A comparison of the PK parameters after the first dose of nivolumab in Study CA209039 to that of Study CA209003 was provided, and is shown below in Table 82. According to the sponsor, the results show that the inter-individual variabilities were similar between these two studies as described by CV%. The sponsor concluded that, while the inter-individual variability of trough concentration samples from cHL were relatively higher compared to derived PK parameters, the overall variability of nivolumab PK in cHL was not greater than that in solid tumours.

Table 82. Summary statistics for PK parameters of nivolumab administered 3 mg/kg Q2W after first dose (Studies CA209003 and CA209039)

	CA209003	CA209039
Cmax (µg/mL)		
Geo.Mean[N]	61.3 [13]	55.7 [18]
(%CV)	(26.4)	(22.8)
AUCtau (µg*h/mL)		
GEO.MEAN[N]	8785.8 [13]	9138.9 [18]
(%CV)	(22.7)	(27.1)

Source: CA209003 CSR[1]

11.2.7.2. Evaluator's response

The response is noted. The evaluator accepts that inter-individual variability in patients with cHL is not worse than that seen in patients with other tumour types.

11.3. Pharmacodynamics

11.3.1. Question 12: Immunogenicity and Studies CA209205 and CA209039

There are some concerning elements to the results of ADA testing in Studies CA209205 and CA209039:

- Baseline positive rate:
  - 7/159 (4.4%) of patients in CA209205 and 3/19 (15.8%) of patients in Study CA209039 tested positive for nivolumab ADA without prior exposure to nivolumab.
- Baseline positive but subsequently negative:
  - 8/10 of patients who tested positive at Baseline, subsequently tested negative for ADA, with this subsequent testing performed within 16 weeks of the baseline test
  - 1/10 recordable titres on multiple occasions but only met the requirement of four-fold increase above baseline on the last occasion testing was performed
  - 1/10 had not had any subsequent testing.

The evaluator notes that 'persistent positive', as defined by the sponsor, requires ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart. The rationale provided for the 16 weeks in between positive samples is 'the long half-life of IgG4'. The negative results on subsequent testing of baseline positive patients are not consistent with this rationale.

- Cause of Hypersensitivity/Infusion reactions
  - There were 26/158 (16.5%) of patients from all cohorts in Study CA209205 and 4/23 (17.4%) of patients in Study CA209039 who had hypersensitivity/infusion reactions reported, none of these patients were ADA positive. As per the Study CA209205 CSR, '*The presence of ADA was not associated with the occurrence of hypersensitivity and/or infusion-related reactions*'. No alternative mechanism by which these reactions occurred was discussed.

Questions:

1. How does the sponsor account for patients who were baseline ADA positive but subsequently ADA negative, despite the repeat testing occurring within the half-life of IgG4 (16 weeks)?
2. Do these findings invalidate the definition used for persistent positive, which is based on this half-life?

3. How does the sponsor account for the high rate of hypersensitivity/infusion reactions reported in the studies?

11.3.1.1. Sponsor's response

The sponsor noted that the 16 week window is the recommended time between assessments for evaluating transient versus persistent positive treatment-induced responses. The positive baseline samples all had low ADA titres (1 to 8) and presumably consisted of pre-existing cross reacting endogenous antibodies. There 8/10 patients who were subsequently negative within 3 to 4 weeks and remained negative. There were 2/10 patients who had multiple ADA positive results over time. The accounting for the varied duration of baseline ADA positive responses is not clear because the origin and nature of the pre-existing ADAs are unknown and there are a variety of natural clearance mechanisms that could be attributed. The sponsor reiterated that the presence of ADAs was not associated with the occurrence of hypersensitivity and/or infusion related reactions because all the subjects who experienced these events were ADA negative

The sponsor re-iterated that the definition of persistent positive treatment-induced ADAs is from the Shankar et al. white paper and that pre-existing ADAs detected in the baseline samples are not treatment-induced ADAs and therefore not relevant to the definition of treatment-induced ADAs.[25]

The sponsor noted that the reported incidence of infusion-related reactions were higher in cHL population than in the nivolumab monotherapy treatment group (3.8%) including subjects with other tumour types. However, this was not considered clinically significant as almost all infusion-related reactions were Grade 1 to 2, all events resolved, and no events led to permanent discontinuation of nivolumab. The reason for the higher incidence in the cHL population remains unclear but appears to be partly attributable to a higher reporting incidence at one site in Germany (11/16 treated Cohort B subjects at the site had infusion-related reactions), which accounted for 64.7% (11/17) of all infusion-related reactions in the Integrated SCE Population.

A summary of infusion related reactions as reported in nivolumab monotherapy studies was provided.

The frequency of infusion-related reactions (any causality) from cHL population was:

- 32 subjects (12.2%) reported from Integrated cHL Population (n = 263)
- 17 subjects (17.9%) in the Integrated SCE Population (n = 95)

The frequency of infusion-related reactions (any causality) in nivolumab monotherapy treatment group from Studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209205 and CA209039 (cHL patients) was:

- 75 subjects (3.8 %) in the nivolumab monotherapy treatment group (n = 1991)
- 43 subjects (2.5 %) in the nivolumab monotherapy treatment group (n = 1728) from solid tumours when cHL patients from Studies CA209205 and CA209039 are excluded.

Additional clinical detail regarding infusion-related reactions in the cHL population was provided:

- No events were fatal and no events led to permanent discontinuation of nivolumab. All subjects were able to continue nivolumab treatment after resolution of the infusion reaction.
- The majority of subjects (75.0%, 24/32) only experienced 1 infusion-related reaction.
- Infusion-related reactions developed early (90.6%, 29/32 subjects with onset of first event on the day of the first infusion (Day 1 of Cycle 1)). In the remaining three, the onset of first

infusion related reaction was Day 1 of Cycle 2 in two subjects and Day 12 of Cycle 2 in one subject.

- 8 subjects received corticosteroids for treatment, and infusion-related reactions resolved in all subjects within 48 hours.

An analysis of delayed hypersensitivity reactions was performed using a broad search to capture anaphylactic reaction, anaphylactic shock, bronchospasm, and hypersensitivity, in addition to infusion related reactions shown below in Table 83.

Table 83. Incidence of hypersensitivity/infusion reactions

Any causality	Integrated cHL Population (n = 263)		Integrated SCE Population (n = 95)		Nivolumab Monotherapy Treatment Group[a] (n = 1991)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Anaphylactic reaction	0	0	0	0	2 (0.1)	2 (0.1)
Anaphylactic shock	0	0	0	0	0	0
Bronchospasm	5 (1.9%)	0	4 (4.2%)	0	10 (0.5)	1 (<0.1)
Hypersensitivity	6 (2.3%)	1 (0.4%)	1 (1.1%)	0	49 (2.5)	2 (0.1)
Infusion related reaction	32 (12.2%)	1 (0.4%)	17 (17.9%)	0	75 (3.8)	3 (0.2)

Source: Appendix HL.5.19.US of Appendix 3

[a] Nivolumab treatment group consists of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209205 and CA209039 (cHL patients)

Clinical descriptions of these events as they occurred in the cHL population were provided:

- Hypersensitivity (any causality); n = 6 out of 263 cHL subjects
  - All hypersensitivities were Grade 1 or 2, except 1 Grade 3 event.
  - No events were fatal and no events led to permanent discontinuation of nivolumab.
  - 2 subjects with hypersensitivities were considered as not related, whereas the remaining 4 subjects with hypersensitivities were considered as related by investigators.
  - 3 subjects experienced delayed onset of hypersensitivities, with onset 6 months from the first infusion of nivolumab.
  - 3 subjects required dose delay, while no dose change was reported in the remaining 3 subjects.
  - 1 subject with Grade 3 hypersensitivity received prednisone for treatment, and the event resolved in 43 days.
  - Descriptions of 'hypersensitivity' as experienced by individual patients were: pruritus or itching (n = 2), itchy and runny nose (n = 1), maculopapular rash (n = 1), 'hypersentivity reaction' (n = 1) and 'allergic reaction' (n = 1). The dose was delayed in 3 patients (pruritus, allergic reaction and hypersensitivity reaction). The event was not resolved at time of analysis in 2 patients (itchy and runny nose, maculopapular rash).
- Bronchospasm (any causality); n = 5 out of 263 cHL subjects
  - All Bronchospasms were Grade 1 or 2.
  - No events were fatal and no events led to permanent discontinuation of nivolumab.
  - All 5 bronchospasms were considered as not related by investigators.
  - Bronchospasms can be observed up to almost 1 year from the first infusion of nivolumab.

All patients experiencing these events were ADA negative. The sponsor concluded that delayed hypersensitivity can be observed beyond 6 months from the fist dose of nivolumab at a very low

frequency but that, overall, *'hypersensitivity/infusion reactions are not considered clinically relevant to nivolumab treatment'*.

11.3.1.2. Evaluator's response

The evaluator accepts that ADA status, as currently tested for and defined, is not related to the occurrence of hypersensitivity/infusion reactions. It may therefore be more appropriate to consider these as another manifestation of immune-related adverse reactions. The speculation that Baseline ADA positive status is related to cross-reaction of the assay with endogenous antibodies, and that the changes in subsequent ADA status relates more to these endogenous antibodies rather than antibodies to nivolumab, is of interest. However, it would indicate that the assay used has questionable specificity.

The evaluator does not agree that hypersensitivity/infusion related reactions are not clinically relevant. These reactions may be infrequent but may be serious as shown by the 2 events of anaphylaxis in the nivolumab monotherapy population and may be distressing, as shown by the number of days taken for the events of bronchospasm, pruritus and itching to resolve (20 to 50 days). These events were not apparently assessed as related to nivolumab therapy and no dose delay occurred. If these had been considered treatment related immune related adverse reactions, then dose delay ± corticosteroid treatment may have resulted in a shorter course.

11.3.2. Question 13: PD-L1 expression and Studies CA209205 & CA209039

The definition used for PD-L1 expression in the cHL studies is different from that used in the solid tumour studies. In the solid tumour studies, an evaluable specimen must contain 100 tumour cells per slide, with the estimate of PD-L1 expression determined by the number of tumour cells expressing PD-L1 divided by at least 100. In the cHL studies, PD-L1 expression was calculated by the number of R-S cells expressing PD-L1 divided by the number of R-S cells, with no minimum number of R-S cells. Samples with as few as one R-S cells were considered evaluable. According to a table [not included here] in the CSR for Study CA209205, evaluable samples contained 1 to 4 R-S cells (rare), 5 to 25 R-S cells (moderate) and > 25 R-S cells. If a patient in each of these groupings had only one R-S cell that expressed PD-L1, the estimated expression could range from less than 4% to 100%. Does this not render the results according to PD-L1 expression un-interpretable?

11.3.2.1. Sponsor's response

The sponsor noted that in most cases of histopathological analysis of cHL, number of R-S cells in the tissue section is less than 50 and that, in Study CA209205, 57 of 187 evaluable cases (30%) had less than 25 identifiable R-S cells in the tested slide. The sponsor also confirmed that, using the definition of PD-L1 positive as described above, that most patients were PD-L1 positive regardless of the number of R-S cells. In Study CA209205, when distinguishing based on the frequency of R-S cells, the PD-L1-positive cases were 72 of 73 (99%) in the 'frequent' category, 42 of 47 (96%) in the 'moderate' category, and 7 of 10 (70%) in the rare category.

11.3.2.2. Evaluator's response

The information provided in the sponsor's response suggests that most, but not all, R-S cells express PD-L1 and that grading of PD-L1 expression (by % expression) in cHL is unhelpful. This is further discussed in Question 14 below.

11.3.3. Question 14: PD-L1 expression and R-S cells

Patients in Studies CA209039 and CA209205 appeared to have high estimated PD-L1 expression, suggesting that most R-S cells expressed PD-L1, but this is not clear in the presentation of data in the CSRs. Could the sponsor provide a frequency distribution of the baseline estimated PD-L1 expression by patient number, grouped according to estimated PD-L1 expression of 0%, > 0 to 10%, 11 to 20%, 21 to 30%, 31 to 40%, 41 to 50%, 51 to 60%, 61 to 70%, 71 to 80%, 81 to 90%, 91 to 100%? Could the sponsor provide a breakdown for the 0%

and 91 to 100% groups according to whether the corresponding specimens had rare (1 to 4 R-S cells), moderate (4 to 25 R-S cells), or frequent R-S cells (> 25 R-S cells)?

11.3.3.1. Sponsor's response

The requested analysis was provided.

11.3.3.2. Evaluator's response

The analysis indicates that of the 10 patients with 1 to 4 R-S cells per field, the R-S cells did not express PD-L1 in 3 patients, that for the other 7 patients at least one R-S cell was positive and that for 4/10, all of the R-S cells were positive. In the other groups according to frequency of R-S cells per field:

- in patients with more than 25 R-S cells per field, PD-L1 was expressed on almost all (91 to 100%) of R-S cells in 52/73 (71%) specimens.
- in patients with 5 to 25 R-S cells per field, PD-L1 was expressed on almost all (91 to 100%) of R-S cells in 27/47 (57%) specimens.

This analysis indicates that not all R-S cells express PD-L1. Given the low number of R-S cells that may be visible per field, this raises difficulties in determining PD-L1 expression as it cannot be assumed that the distribution of PD-L1 status in R-S cells across a tumour specimen is uniform.

11.3.4. Question 15: Pharmacodynamic interactions

Patients who developed irARs during, or following treatment, could be treated with immune suppressive therapy/therapies) in Studies CA209205 and CA209039. Theoretically, the use of immunosuppression during treatment with nivolumab could decrease efficacy. Could the sponsor provide separate efficacy analyses for those patients in Studies CA209205 and CA209039 who received immunosuppression for irARs during treatment with nivolumab?

11.3.4.1. Sponsor's response

The sponsor performed additional efficacy analyses on the patients who developed irARs during or following treatments and were being treated with immune-suppressive therapies for the SCE population from Studies CA209205 and CA209039 (Cohort B and ASCT-BREN failed group). Tabulated results of BOR, ORR, PFS, TTR and DOR for patients who received immunosuppressive therapy compared to patients who did not receive immunosuppressive therapy. There were 26 patients in the SCE population who received immunosuppression (Group1), compared to 69 who did not (Group 2). There were 15 responders in group 1 and 48 in Group 2: the ORR was 57.7% (95% CI 36.9, 76.6) for group 1 and 69.6% (95% CI 57.3, 80.1) for Group 2. The median PFS was 11.3 months (95% CI 7.75, NA) for Group 1 and 15 months (95% CI 11.60, NA) for Group 2. The sponsor concluded that the efficacy between the two groups was comparable.

11.3.4.2. Evaluator's response

The sponsor's analysis has found a numerically lower ORR per IRRC in the 26 patients who received immunosuppressive therapy compared to the 69 who did not but substantial overlap of the 95% CI (57.7% (95% CI 36.9, 76.6) compared to 69.6% (95% CI 57.3, 80.1)). Median PFS was also lower in the sub-group treated with immunosuppression (11.33 months compared to 14.95 months. This s a post-hoc analysis of a small number of patients but does create uncertainty regarding a potential reduction in the efficacy of nivolumab when co-administration of immunosuppressive therapy is required.

11.4. Efficacy

11.4.1. Question 16: Updated results from Study CA209039 and Study CA209205

The sponsor's assessment of efficacy is based on the interim results from 2 small exploratory Phase I and Phase II studies using the surrogate end-points of objective response rate. Database lock for the interim analyses for both studies was August 2015. Could the sponsor provide updated efficacy results for both of these studies? These updated results should include:

- Nivolumab exposure: median (min, max) number of doses, cumulative dose, estimated median duration of treatment for Cohort B of Study CA209205.
- Updated ORR, TTR, DOR, PFS and OS for Cohort B for Study CA209205.
- Updated PFS and OS for the ASCT-Bren Failed population for Study CA209039.

11.4.1.1. Sponsor's response

The sponsor provided updated clinical data based on a minimum of 12 months follow-up of subjects enrolled in Cohort B of Study CA209205.

The primary endpoint analysis for Study CA209205 Cohort B included in the submission was based on the 5 October 2015 DBL (20 Oct 2015 for efficacy per IRRC; data cut-off date of 20 August 2015) with median follow-up of 8.92 months and is referred to as the 'October 2015 DBL analysis'. The updated efficacy analysis for Study CA209205 Cohort B was based on the 19 April 2016 DBL (14 June 2016 for efficacy per IRRC; data cut-off date of 14 March 2016) after a minimum follow-up of 12 months (median follow-up of 15.44 months) and is referred to as the 'April 2016 DBL analysis'.

An updated summary of exposure for the patients in Study CA209205 was provided, shown in Table 84 below.

Table 84. Study CA209205 Extent of nivolumab exposure, all treated subjects, Cohort B

	April 2016 Database Lock	October 2015 Database Lock
	Cohort B (N = 80)	Cohort B (N = 80)
Number of Doses Received		
Median (Min - Max)	27.0 (3 - 41)	17.0 (3 - 25)
Cumulative Doses (mg/kg)		
Median (Min - Max)	80.59 (9.0 - 122.3)	50.88 (9.0 - 75.8)
Relative Dose Density		
≥110%	0	0
90% to <110%	55 (68.8)	61 (76.3)
70% to <90%	21 (26.3)	16 (20.0)
50% to <70%	4 (5.0)	3 (3.8)
<50%	0	0
Duration of Treatment (Months)		
Events	37	29
Median (95% CI)	N.A. (9.26, N.A.)	N.A. (9.26, N.A.)

The updated efficacy results for Study CA209205 as provided by the sponsor are shown below in Table 85.

Table 85. Study CA209205 Updated efficacy results summary side-by-side with that from the earlier database lock, all treated subjects, Cohort B

	April 2016 Database Lock (Median Follow-up = 15.44 Months)		October Database Lock (Median Follow-up = 8.92 Months)	
Efficacy Parameter	IRRC N = 80	Investigator N = 80	IRRC N = 80	Investigator N = 80
ORR[a]				
Number (%) of Responders	54 (67.5)	60 (75.0)	53 (66.3)	58 (72.5)
Exact 95% CI	56.1, 77.6	64.1, 84.0	54.8, 76.4	61.4, 81.9
DOR[b]				
Events[c]	18/54	15/60	11/53	9/58
Median (95% CI) (Months)[d]	13.14 (8.74, N.A.)	N.A. (9.56, N.A.)	7.79 (6.64, N.A.)	9.10 (6.74, N.A.)
Min, Max[e]	0.0+, 14.2+	0.0+, 14.2+	0.0+, 9.5+	0.0+, 9.5+
Median TTR (Months)[d]	2.10	2.23	2.10	2.17
Min, Max (Months)	1.6, 11.1	1.6, 14.7	1.6, 5.7	1.6, 9.1
CR Rate				
Number (%) of Responders	6 (7.5)	26 (32.5)	7 (8.8)	22 (27.5)
Exact 95% CI[f]	2.8, 15.6	22.4, 43.9	3.6, 17.2	18.1, 38.6
Duration of CR				
Events[c]	1/6	2/26	1/7	1/22
Median (95% CI) (Months)[d]	N.A. (4.63, N.A.)	N.A. (8.74, N.A.)	4.63 (N.A., N.A.)	8.74 (N.A., N.A.)
Min, Max (Months)[e]	0.7+, 10.4+	0.0+, 11.8+	0.7+, 4.6	0.0+, 8.7
PR Rate				
Number (%) of Responders	48 (60)	34 (42.5)	46 (57.5)	36 (45.0)
Exact 95% CI[f]	48.4, 70.8	31.5, 54.1	45.9, 68.5	33.8, 56.5
Duration of PR				
Events[c]	17/48	13/34	10/46	8/36
Median (95% CI) (Months)[d]	13.14 (7.79, N.A.)	10.09 (6.51, N.A.)	7.79 (6.64, N.A.)	7.79 (6.74, 7.79)
Min, Max (Months)[e]	0.0+, 13.4+	0.0+, 13.1+	0.0+, 9.5+	0.0+, 7.8
PFS (Months)				
Median (95% CI)[d]	14.78 (11.33, N.A.)	N.A. (11.33, N.A.)	9.99 (8.41, N.A.)	10.94 (9.99, 11.56)
PFS Rate (95% CI)[d], %				
At 6 Months	79.8 (68.6, 87.3)	82.1 (71.1, 89.2)	76.9 (64.9, 85.3)	82.6 (71.1, 89.8)
At 12 Months	54.6 (40.9, 66.4)	55.9 (41.9, 67.8)	N.A.	N.A.
OS (Months)				
Median (95% CI)[d]	N.A.		N.A.	
OS Rate (95% CI)[d], %				
At 6 Months	97.5 (90.2, 99.4)		98.7 (91.0, 99.8)	
At 12 Months	94.9 (86.9, 98.0)		N.A.	

[a] CR + PR as per the 2007 IWG criteria, confidence interval based on the Clopper and Pearson method. FDG-PET scan was required for confirmation of radiographic CR. Additionally, subjects with lymphoma involvement in bone marrow at study entry required bone marrow aspirate and biopsy to confirm radiographic CR.

[b] Determined for subjects with CR or PR.

[c] Events were progression or death.

[d] Computed using Kaplan-Meier method.

[e] For responders who did not have reported progression or death date, DOR was censored at the last tumor assessment date and is denoted by a + symbol.

[f] Confidence interval based on the Clopper and Pearson method.

An updated analysis of efficacy for the Integrated SCE population (N = 95) was provided. A separate update for the patients in Study CA209039 was not provided. According to the sponsor *'No updated analysis was performed for the CA209039 ASCT-Bren Failed subjects, since mature efficacy data with a median follow-up of 21.88 months were presented previously'.*

Comment: An interim report for Study CA209039 was provided in the sponsor's application. Follow-up in Study CA209039 for the 23 cHL subjects was reported to range from 7.3 to 27.8 months (Study CA209039 CSR). An exploratory objective of this study

was '*To assess the overall survival up to five years for the monotherapy nivolumab*'. Updated results for PFS and overall survival provided separately for the 15 ASCT-Bren Failed sub-group were specifically requested by the evaluator due to concerns regarding the combination of patients from the two studies. These results have not been provided.

Table 86. Updated efficacy results summary side-by-side with that from the earlier database lock, integrated SCE population

	April 2016 Database Lock (Median Follow-up = 15.77 Months)		October 2015 Database Lock (Median Follow-up = 9.46 Months)	
Efficacy Parameter	**IRRC N = 95**	**Investigator N = 95**	**IRRC N = 95**	**Investigator N = 95**
ORR[a], n (%)	63 (66.3)	73 (76.8)	62 (65.3)	71 (74.7)
95% CI	55.9, 75.7	67.1, 84.9	54.8, 74.7	64.8, 83.1
DOR[b]				
Events/Responders[c]	22/63	18/72	15/62	12/70
Median (95% CI) (Months)[d]	13.14 (9.46, N.A.)	N.A. (15.51, N.A.)	8.74 (6.83, N.A.)	15.51 (8.25, NA)
Min, Max (Months)[e]	0.0+, 23.1+	0.0+, 23.1+	0.0+, 23.1+	0.0+, 23.1+
CR Rate, n (%)	6 (6.3)	28 (29.5)	7 (7.4)	24 (25.3)
95% CI[f]	(2.4, 13.2)	(20.6, 39.7)	(3.0, 14.6)	(16.9, 35.2)
Duration of CR				
Events/Responders[c]	1/6	2/28	1/7	1/24
Median (95% CI) (Months)[d]	N.A. (4.63, N.A.)	N.A. (8.74, N.A.)	4.63 (N.A., N.A.)	N.A. (8.74, N.A.)
Min, Max (Months)[e]	0.7+, 10.4+	0.0+, 15.0+	0.7+, 4.6	0.0+, 15.0+
PR Rate, n (%)	57 (60.0)	45 (47.4)	55 (57.9)	47 (49.5)
95% CI[f]	(49.4, 69.9)	(37.0, 57.9)	(47.3, 68.0)	(39.1, 59.9)
Duration of PR				
Events/Responders[c]	21/57	16/44	14/55	11/46
Median (95% CI) (Months)[d]	13.14 (8.74, N.A.)	15.51 (7.39, N.A.)	8.74 (6.83, N.A.)	15.51 (6.74, N.A.)
Min, Max (Months)[e]	0.0+, 23.1+	0.0+, 23.1+	0.0+, 23.1+	0.0+, 23.1+
Median TTR (Months)[d]	2.04	2.17	2.07	2.10
Min, Max (Months)	0.7, 11.1	0.7, 14.7	0.7, 5.7	0.7, 9.1
Median Time to CR (Months)[d]	4.11	5.68	4.44	4.75
Min, Max (Months)	3.3, 6.9	1.6, 19.9	3.3, 6.9	1.6, 19.9
Median Time to PR (Months)[d]	1.97	1.95	1.94	1.94
Min, Max (Months)	0.7, 11.1	0.7, 14.7	0.7, 5.7	0.7, 9.1
PFS (Months)				
Median (95% CI) (Months)[d]	14.78 (11.33, N.A.)	21.19 (11.83, N.A.)	12.55 (8.54, N.A.)	21.19 (9.99, N.A.)
PFS Rate (95% CI)[d], %				
At 6 Months	79.5 (69.4, 86.6)	82.5 (72.6, 89.1)	76.8 (65.8, 84.7)	83.0 (72.9, 89.7)
At 12 Months	57.1 (44.7, 67.7)	59.0 (46.3, 69.6)	N.A.	N.A.
OS (Months)				
Median (95% CI)[d]	N.A.		N.A. (21.13, N.A.)	
OS Rate (95% CI)[d], %				
At 6 Months	97.9 (91.7, 99.5)		98.9 (92.5, 99.8)	
At 12 Months	94.5 (87.3, 97.7)		N.A.	

[a] CR + PR as per the 2007 IWG criteria, confidence interval based on the Clopper and Pearson method. FDG-PET scan was required for confirmation of radiographic CR. Additionally, subjects with lymphoma involvement in bone marrow at study entry required bone marrow aspirate and biopsy to confirm radiographic CR.

[b] Determined for subjects with CR or PR.

[c] Events were progression or death.

[d] Computed using Kaplan-Meier method.

[e] For responders who did not have reported progression or death date, DOR was censored at the last tumor assessment date and is denoted by a + symbol.

[f] Confidence interval based on the Clopper and Pearson method.

The sponsor's response included the following statements:

- *'The PFS and OS results to date also support highly relevant clinical outcomes in cHL patients receiving nivolumab.*
- *Based on the updated efficacy analyses, [the sponsor] proposes a modified version of the note to indication suggested by the Clinical Evaluator (see the response to Question 39):*
  - *Note to cHL indication: The approval of this indication is on the basis of overall response rate. Data on progression free survival and overall survival is limited.'*

11.4.1.2. Evaluator's response

The evaluator notes that in the response to Question 20 (below) the sponsor stated: '*A subsequent DBL for all 3 cohorts took place on 28 June 2016 after requisite minimum follow-ups for Cohorts A (9 months) was met*' and that safety data from this DBL has been provided in response to Question 26. It is not clear as to why updated efficacy results for Cohort B from this analysis have not been provided, instead of repeating the April 2016 DBL efficacy data provided to the EMA. The evaluator also noted that the June 2016 DBL analysis for Cohorts A and C was earlier than that described in the study protocol provided in the submission. According to the protocol, analysis of Cohort A and C was to occur after a minimum follow-up period of 12 months.

From the data provided with the April 2016 DBL:

- The median number of doses received by the patients in Cohort B of Study CA209205 had increased from 17 to 27 and the median duration of therapy had still not been reached.
- The primary end-point for Study CA209205 was ORR per IRRC.

Table 87. Updated results for primary endpoint

	Result Per IRRC April 2016 Median follow-up 15.4 months	**Result Per IRRC October 2015** Median follow-up 8.9 months
Efficacy parameter	Cohort Bb (n = 80)	Cohort Bb (n = 80)
ORR (95% CI)	67.5% (56.1, 77.6)	66.3% (54.8, 76.4)
Number of responders (CR + PR)	54	53
No with CR	6	7
No with PR	48	46
No with SD		18

With the longer follow-up, there has been one less patient with complete response and 2 more patients with partial response. The ORR was similar at both time points, although numerically higher at the longer follow-up.

Secondary outcome measures were DOR, CR rate and duration of CR, PR rate and duration of PR as assessed by IRRC; Investigator assessed ORR and DOR. PFS per IRRC, OS. As shown in the sponsor's response, the median duration of response per IRRC had increased from 7.8 months to 13.1 months, with the longer follow-up. Median PFS per IRRC had also increased from 10 months to 14.8 months and median OS had not been reached.

The results for the SCE population are shown below. OS results remain immature at the median follow-up of 15.44 months. The median PFS is numerically longer.

Table 88. Results per IRRC as per interim CSRs and updated analysis

	All patients April 2016	All patients Oct 2015	CA209205 April 2016	CA 209039 August 2015	CA209205 October 2015
	(n = 95)	(n = 95)	Cohort B (n = 80)	ASCT-Bren Failed Group (n = 15)	Cohort B (n = 80)
Median follow-up (months)	15.77	9.46	15.4	23.3	8.9
Median number of nivolumab doses (range)			27 (3 to 41)	24 (6 to 48)	17 (3 to 35)
Efficacy parameter					
ORR (95% CI)	66.3%	62% (55, 75)	67.5% (56.1, 77.6)	60% (32.3, 83.7)	66.3% (54.8, 76.4)
No with CR (%)		7	6	0	7
No with PR		55	48	9	46
DOR (months)[b]					
Median[a] (95% CI)	N.A. (4.63, N.A.)	8.74 (6.83, NA)	13.14 (8.74, N.A.)	11.96 (1.84, NA)	7.79 (6.64, NA)
Min, Max	0.0+, 23.1+	0.0, 23.1+	0.0+, 14.2+	1.8, 23.1+	0.0+, 9.5+
PFS (months)[b]					
Median[a] (95% CI)	14.78 (11.33, N.A.)	12.55 (8.54, NA)	14.78 (11.33, N.A.)	12.65 (5.91, NA)	9.99 (8.41, NA)
OS (months)[b]					
Median[a] (95% CI)	NA	NA (21.13, NA)	NA	NA (15.84, NA)	NA

The symbol + indicates a censored value. a) KM estimate; b) Duration of treatment, PFS and OS results in CA209205 Cohort B were immature with median not reached; OS was immature with median not reached

The updated efficacy results are consistent with those reported at the earlier analysis, with similar ORR and numerically higher PFS. Overall survival rates are immature at follow-up of 15.7 months.

With regards to the wording of the Note to Indication, the evaluator is of the opinion that the wording proposed by the sponsor is not appropriate as it may be interpreted as meaning that there is limited evidence of an improvement in PFS and OS. The sponsor has not demonstrated an improvement in OS or PFS compared to historical controls. According to the sponsor's Clinical Overview, and based on current understandings, *'The median OS of patients who relapse after ASCT was initially reported to be < 1 year; more recent data suggests that the median OS is evolving and may be closer to 2 years because of the availability of newer therapies like brentuximab*'. The results for PFS and the immature result for overall survival after median follow-up of 15.7 months in the two single arm open label studies are inadequate for any conclusions to be reached regarding the potential effect of nivolumab on these measures. The evaluator proposes the following alternative, including that the wording 'Note to Indication' be included for consistency with other TGA-approved PIs:

'Note to Indication: The approval for this indication is on the basis of objective response rate. An improvement in progression free survival or overall survival has not been demonstrated'. See also Question 39, below.

11.4.2. Question 17: Dose escalation phase of Study CA209039

The primary objective of Study CA209039 was '*To establish the dose limiting toxicities, maximum tolerated dose and recommended Phase II dose for nivolumab up to a maximum of 3 mg/kg administered every 2 weeks to patients with relapsed/refractory hematologic malignancy*.' According to the study design, '*At the dose expansion cohorts, approximately 23 patients are expected to be enrolled in each of four tumour types and treated at the previously determined MTD or if no MTD is identified a maximum dose of 3 mg/kg*.' The interim CSR reports the results of the HL/PMBL expansion cohort, with these patients treated at 3mg/kg.

Could the sponsor provide further information regarding the dose escalation phase? This should include:

- the number of patients involved and their haematological conditions.
- duration of nivolumab therapy.
- if a dose limiting toxicity occurred in any patient and if a MTD was identified.
- the reason(s) for Amendment 02 of the protocol (December 2012) which eliminated the highest (10 mg/kg) of three dose levels scheduled to be examined.

11.4.2.1. Sponsor's response

According to the sponsor's response, there were 13 patients involved in the dose escalation phase with 6/13 receiving the dose of 1 mg/kg and 7 receiving 3 mg/kg. All of the patients had haematological malignancies:

- Of the 6 who received 1 mg/kg, 3 had B cell lymphoma (diffuse large B cell: n = 1; follicular: n = 1; other: n = 1) and 3 had multiple myeloma.
- Of the 7 subjects who received 3 mg/kg dose, 2 had cHL, 3 had B cell lymphoma (diffuse large B cell: n = 2; other: n = 1), 1 had multiple myeloma, and 1 had chronic myelogenous leukaemia

The number of doses received ranged from 1 to 44 in both 1 mg/kg and 3 mg/kg cohorts. The duration of treatment ranged from 0.1 to 95.1 weeks in the 1 mg/kg cohort and from 0.1 to 89.1 weeks in the 3 mg/kg cohort. No DLT occurred and no MTD was identified.

The Amendment 02 for Study CA209039 eliminated the highest (10 mg/kg) of three dose levels based on the results from Phase I Study CA209003 in solid tumours which indicated that the probability of a tumour response tended to approach a plateau for trough concentrations produced by 3 mg/kg and 10 mg/kg administered Q2W. In this study, nivolumab was 'adequately tolerated' up to 10 mg/kg, the highest dose tested, and no MTD was identified. However, the 10 mg/kg dose level had numerically higher frequencies of Grade 3/4 drug-related SAEs and AEs leading to discontinuation. A dose of 3 mg/kg Q2W was selected as the dose anticipated to achieve an appropriate balance of benefit and risk

11.4.2.2. Evaluator's response

Of note is that there were no DLT reported, a MTD was not identified and the decision to not proceed with the dose level of 10 mg/kg was not the result of a new safety signal identified in the dose escalation phase of Study CA209039 but based on the results of Phase I Study CA209003. It is also of interest that patients in Study CA209003 who had higher nivolumab exposure, with the dose of 10mg/kg, experienced numerically higher frequencies of Grade 3/4 drug-related SAEs and AEs leading to discontinuation.

11.4.3. Question 18: Study conduct in Study CA209205

The format CA209-205-xx-yyy is used for the patient ID number, with xx representing a 2 digit number and yyy representing a 3 digit number. The evaluator notes that 27 of the 65 reported protocol deviations for Cohort B have the same xx number (-33-). If this –xx- number represents the investigational site, then site 33 is over-represented in the listing of significant protocol deviations, with 27/65 reports (42%) involving 19 patients. These protocol deviation reports included tumour assessments outside the protocol defined window (6), delayed notification of SAEs (2), administration of nivolumab over approximately 30 minutes instead of 60 minutes (3), delayed submission of local laboratory results (15) and use of an inappropriate language consent form (1). There was also one 'relevant' protocol deviation that occurred at this site, a patient without measurable disease was enrolled in the study (in Cohort C). The evaluator also notes that 6/14 reported relevant protocol deviations, also involving enrolment of patients without measurable disease, were reported from Site 35.

Significant protocol deviations were defined as study conduct that differed significantly from the protocol, including GCP noncompliance. Relevant protocol deviations were defined as having the potential to affect the interpretability of study results.

The number and variety of protocol deviations at Site 33 raise concerns regarding study conduct at this site. It is also notable that adverse event reporting appeared to be different at this site, with the sponsor's SCS noting '*a high incidence of infusion-related reactions that occurred at one CA209205 study center in Germany (15/30 treated patients at the site had infusion related reactions), which accounted for 46.9% (15/32) of all infusion-related reactions in CA209205. Consequently, the observed incidence of infusion reactions in CA209205 was higher in Europe (18.3%) than in US/Canada (7.0%)'.* From the subject ID numbers in the narratives provided for IMAE in the CA209205 CSR, this study centre in Germany is site 33. The number of inappropriately enrolled patients at site 35 raises concerns regarding study conduct at this site.

From the list of investigators provided in Appendix 1.5, 30 patients were treated at site 33 and 25 at site 35. From the by-subject listings provided, 16 of the patients in Cohort B were treated at Site 33 and 5 patients at site 35. The efficacy results of this interim analysis of Study CA209205 are based on the results of the 80 patients in Cohort B of the study. It is concerning that 21/80 patients were treated at two sites with questionable study conduct.

Could the sponsor confirm if the –xx- in the patient ID number refers to the investigational site at which the patient was enrolled?

If the –xx- in the patient ID number does refer to the investigational site at which the patient was enrolled, the sponsor is asked if sites 33 and 35 audited during the study and, if so, what were the results of these audits – in particular were any specific concerns regarding study conduct at these sites raised? Could the sponsor also indicate if the audit(s) were conducted by an independent group?

If the –xx- in the patient ID number does refer to the investigational site at which the patient was enrolled the sponsor is requested to perform a sensitivity analysis for the primary efficacy outcome measure (ORR by IRRC in cohort B) with the results from sites 33 and 35 excluded from the analysis. This should include any updated efficacy results.

11.4.3.1. Sponsor's response

The sponsor confirmed that the –xx- in the patient ID number referred to the study site.

With regard to the patients who were reported to be inappropriately enrolled at sites 33 and 35 ('no measurable disease or FDG avid'), according to the interim CSR for Study CA209205, this had resulted from 'incomplete data clean-up' for Cohorts A and C for the interim report. A subsequent database lock for an interim analysis of all 3 cohorts took place on June 2016 and '*Based on the updated information at this DBL, there were no relevant protocol deviations due to 'No Measurable Disease or FDG Avid.''*

With regard to infusion related reactions a summary of the investigations of the sponsor into the high incidence of these events at Site 33 was provided. This is discussed below, see Question 33: Defining infusion related reactions.

With regard to study conduct at Site 33, a description of a routine site audit by the sponsor's Research and Development Quality department conducted in February 2015 was provided. This department was described as *'an independent group of QA professionals, who conduct GCP audits at investigator sites as well as GCP audits of vendors and internal processes'* and that it *'reports directly to the Head of the Research and Development organization and is independent of the functional groups who are initiating, conducting and reporting clinical trials*'. At the time of the audit, 21 patients had been enrolled and 20 randomised (15 in Cohort B; 5 in Cohort A) and most had been on study for around 3 months.

According to the sponsor's response, the audit at Site 33 resulted in no critical findings which adversely affected the rights, safety or wellbeing of patients and/or the quality and integrity of data. However, areas for improvement were noted in administrative issues, with a backlog in CRF completion and delay in sending of lab reports. This was apparently being addressed by the appointment of 2 additional data managers at the site.

A sensitivity analysis with the patients from Site 33 excluded was provided and has been summarised below in Table 89.

Table 89. Sensitivity analysis with Site 33 patients excluded

	Result Per IRRC April 2016	Result Per IRRC April 2016
Efficacy parameter	Cohort B (n = 80)	Cohort B excluding Site 33 (n = 64)
ORR (95% CI)	67.5% (56.1, 77.6)	64.1% (51.1, 75.7)
Number of responders (CR + PR)	54	41
Number with CR	6	5
Number with PR	48	36

There was a higher proportion of responders at Site 33 (1 CR and 12 PR) giving an ORR for that site of 81.3%.

In the investigation of the high rate of infusion reactions at Site 33, a limited analysis of the patients enrolled at Site 33 was performed. This found that patients with Stage IV disease in Cohorts B and C were over-represented at Site 33: 93.8% in Cohort B at Site 33 compared to 67.5% across all sites.

The higher ORR at Site 33 was attributed to small numbers by the sponsor but also as suggesting that disease burden or the occurrence of infusion related reactions had no adverse impact on ORR.

11.4.3.2. Evaluator's response

The sponsor's response has indicated that issues at Site 33 were largely administrative and that this was confirmed by a 2 day site audit performed by an 'independent' group within the sponsor organisation. The requested sensitivity analysis showed no major change in the ORR with the patients from Site 33 excluded.

It is, however, concerning that 'incomplete data clean-up' had been performed for a study being submitted for regulatory consideration.

11.4.4. Question 19: Exclusion criteria of patients with interstitial pneumonitis, ECOG > 1 and generalisability of results

Patients with interstitial pneumonitis or ECOG status > 1 were excluded from both Study CA209039 and Study CA209205. First line treatment regimens for cHL include bleomycin. Interstitial lung disease is reported in up to 10% of patients treated with bleomycin. Patients who have relapsed cHL after ASCT and brentuximab vedotin have also experienced multiple treatment regimens prior to ASCT, with the effects of these potentially affecting ECOG status.

1. The sponsor is asked to provide an estimate of the proportion of relapsed cHL patients who would be excluded from the studies due to interstitial pneumonitis or ECOG status > 1 and if this may affect the generalisability of the results of this study to the post-approval population.
2. The sponsor is also asked to provide more detail regarding the 36 patients who were enrolled in Study CA209205 but who were not treated, including whether these patients were excluded from treatment due to the presence of interstitial lung disease or ECOG > 1.

11.4.4.1. Sponsor's response

The sponsor notes that '*It is not possible to estimate the proportion of relapsed cHL patients who would have been excluded due to ECOG status > 1 or active interstitial pneumonitis, since these were clearly specified as exclusion criteria in the study protocol, subjects with poor ECOG status or active interstitial pneumonitis, if any, were not considered for enrolment, and relevant information not captured.*'

Of the 36 patients who were enrolled but not treated, 25 were excluded from receiving treatment, because they did no longer meet study criteria. None of the exclusions were reported as due to poor ECOG performance status. None of the exclusions were reported as due to active interstitial pneumonitis but there were 4 patients excluded due to insufficient diffusing capacity of the lung for carbon monoxide (DLCO). Per protocol, a pulmonary function test prior to study enrolment was mandated for subjects with prior history of chemotherapy, or radiation induced pulmonary toxicity.

The sponsor notes that the proposed PI describes special population excluded from the clinical studies, including patients with a baseline performance score ≥ 2 and cHL patients with symptomatic interstitial lung disease.

11.4.4.2. Evaluator's response

The evaluator accepts that no estimate of the target population who may be excluded due to active interstitial lung disease secondary to prior therapy can be provided by the sponsor. Appropriate wording in the PI and ready access to the full PI will be required to ensure that clinicians are aware that '*nivolumab should be used with caution in these populations after careful consideration of the potential benefit-risk on an individual basis*'.

11.4.5. Question 20: Inclusion of patients without measurable disease in Study CA209205

According to a table [not included here], there were 14 patients who were incorrectly enrolled in Study CA209205, with all 14 patients having 'No measurable disease or FGD-avid'. According to the CSR, two patients were in Cohort A, one was in Cohort B and 11 were in Cohort C. There was one other relevant protocol deviation; a patient in Cohort C received concurrent anti-tumour therapy during treatment with nivolumab. The CSR concluded that these protocol deviations would not affect the interpretability of study results as *'the no measurable disease/FDG-avid lesion deviations in Cohorts A and C do not affect study results reported in this interim CSR, since efficacy analysis in these Cohorts were not performed.'* However, efficacy analysis in Cohort B is an integral part of the submission and it is possible that inclusion of one patient who did not meet enrolment criteria for measurable/active disease could potentially affect the results of this analysis. Could the sponsor please advise if a sensitivity analysis has

been performed with this patient excluded? If yes, could the result of this analysis be provided? If no, could such an analysis be conducted or a justification for not doing so please be provided?

11.4.5.1. Sponsor's response

According to the sponsor's response, and as described above in the response to Question 18, protocol deviations in Cohort A and C due to not having measurable disease/FDG-avid lesion at Baseline reported at the October 2015 DBL resulted from incomplete data clean-up. Data clean-up was apparently only performed for Cohort B as efficacy analyses were only to be reported for this cohort in the interim analysis. A subsequent DBL in June 2016 found no subjects without measurable disease/FDG avid lesion in Cohorts A and C.

With regard to the patient in Cohort B who was reported in the interim CSR to have been enrolled without measurable disease/FDG avid lesion, this report was apparently based on erroneous reporting by the investigator. It was subsequently discovered that FDG-PET images taken at screening had been submitted and that these showed an FDG-avid lesion (as determined by the IRRC). The requested sensitivity analysis was not performed as this patient was found to not be a relevant protocol deviation.

11.4.5.2. Evaluator's response

The evaluator is of the opinion that complete data clean-up and confirmation of relevant protocol deviations should be performed prior to submitting a CSR (interim or final) to a regulatory agency.

The evaluator accepts the assertion of the sponsor that the report of the patient in Cohort B as having no measurable disease at Baseline was erroneous and that a sensitivity analysis excluding this patient is not indicated.

11.4.6. Question 21: Response evaluable patients in Study CA209205

The primary analysis of ORR by IRRC was supported by the sensitivity analysis of all response evaluable patients. According to the interim CSR, there were 74 'response evaluable patients'. The evaluator could not identify a clear accounting of the 6/80 patients who apparently did not meet the definition of 'response evaluable patients', although there were 3 patients for whom post-baseline studies were not available and one patient in whom the baseline study showed 'No measurable disease or FDG-avid'.

Could the sponsor:

1. confirm that these four patients were included in the 6 patients who did not meet the criteria for 'response evaluable patients'; and
2. provide a listing of all 6 patients who did not meet the criteria for 'response evaluable patients' together with a description of how each failed to meet the criteria for 'response evaluable patients'?

11.4.6.1. Sponsor's response

The sponsor confirmed that the 4 subjects indicated by the evaluator including 3 without measurable disease were among the 6 patients who did not meet the criteria for 'response evaluable patients' per IRRC.

According to the information provided by the sponsor, the other 2 patients did not meet the criteria for response evaluable disease at Baseline as per the adjudicating radiologist.

The BOR for the 6 patients was provided: NE in 3 and SD in 3.

11.4.6.2. Evaluator's response

The sponsor's response is noted.

11.4.7. Question 22: Treatment beyond progression in Study CA209205

During Study CA 290205, there were 23 patients who developed progressive disease, according to the 2007 IWG criteria as assessed by the investigators. The study protocol allowed for the continuation of treatment in patients with progression at the discretion of the investigator. Of the 23 patients, 9 patients continued nivolumab therapy. The evaluator was unable to find a description of these 9 patients compared to the 12 patients with progression who did not receive ongoing treatment. Could the sponsor please provide a comparison of these patients in terms of factors present at the time of first progression that resulted in 9 patients receiving ongoing treatment but the other 12 patients not receiving ongoing treatment. Could the outcome of the 2 groups of patients also be compared?

11.4.7.1. Sponsor's response

The sponsor provided the clarifications that:

- there were 23 patients who developed disease progression per independent radiologic review committee (IRRC) versus 16 patients who progressed per investigator.
- any decision for the treatment beyond progression was made by investigator in consultation with the sponsor's Medical Monitor and the following criteria were taken into account:
  - the patient was obtaining clinical benefit as determined by the investigator
  - disease progression was not rapid
  - the study drug was tolerated
  - performance status was tolerated
  - other necessary interventions would not be delayed.

A comparison of the 9 patients treated beyond progression and the 7 patients who were not was provided for the characteristics of age, gender and race. According to these characteristics there was no apparent difference. A comparison of outcome in terms of overall survival was provided. In total, there was one patient who died among 7 patients not treated beyond progression, and no patient died among 9 patients treated beyond progression.

11.4.7.2. Evaluator's response

The evaluator acknowledges that the number of patients with disease progression per investigator was 16 and not 23.

The comparison of the 9 patients who received ongoing nivolumab treatment to the 7 patients who did not only considered age, gender and race and found no difference. It is still not clear to the evaluator as to how and why some patients with disease progression were assessed as suitable for ongoing treatment and others were not.

11.4.8. Question 23: Treatment beyond progression in Study CA209039

According to the PFS analysis in Study CA209039, there were 7/23 patients who had progressed (according to the 2007 IWG criteria as assessed by the investigators) or died. Of these, 4/23 patients were treated beyond disease progression. It is not clear to the evaluator how the decision was made to continue treatment in these 4 patients. Could the sponsor please clarify?

11.4.8.1. Sponsor's response

The sponsor provided a similar clarification as that provided in response to Question 22 above, that the decision to continue study therapy after an initial investigator assessed progression was because the investigators in consultation with the Sponsor's Medical Monitor determined that these 4 patients they were felt to be deriving clinical benefit and were tolerating the study drug.

The additional information provided was that written informed re-consent of patients prior to receiving additional treatment with nivolumab was required.

11.4.8.2. Evaluator's response

No patient specific information was provided. Based on the information provided in the interim CSRs and in response to these questions, the benefit or otherwise of continuing treatment after disease progression cannot be determined.

11.4.9. Question 24: Sensitivity analysis of DOR in Study CA209205

In both the primary analysis of DOR and in the sensitivity analysis, patients who had not progressed or died but who had received subsequent anti-cancer therapy were censored. Of the 13 patients who received subsequent anti-tumour therapy, 9 achieved BOR of CR or PR. The sponsor is asked to repeat the sensitivity analysis with these patients counted as having an event instead of being censored. This should be performed on the updated efficacy data as requested in Question 16, above.

11.4.9.1. Sponsor's response

The requested sensitivity analysis of the DOR was performed by considering subjects who didn't progress but receive subsequent anticancer therapy as events, shown in Table 90 below. The event time was the date of the subsequent anticancer therapy.

Table 90. Duration of response per IRRC, sensitivity analysis (All SCE responders per IRRC)

	CA209205 Cohort B + CA209039 cHL: ASCT-Bren Failed N = 63	CA209205 Cohort B N = 54	CA209039 cHL: ASCT-Bren Failed N = 9
DURATION OF RESPONSE (MONTHS)			
MIN, MAX (A)	0.0+, 23.1+	0.0+, 14.2+	1.8, 23.1+
MEDIAN (95% CI) (B)	11.01 (7.46, N.A.)	12.58 (7.46, N.A.)	11.01 (1.84, N.A.)
N EVENT/N RESP (%)	31/63 (49.2)	25/54 (46.3)	6/9 (66.7)

11.4.9.2. Evaluator's response

The duration of response in the Cohort B responders when subsequent anti-cancer therapy is counted as an event is 12.58 months and comparable to the 13.14 months reported when these patients were censored.

11.4.10. Question 25: Clinical relevance

The studies presented by the sponsor indicate an ORR per IRRC of 60% (with a CR rate of 0 and 8.7%), median DOR of 10-12 months and median OS not reached in either study. In the absence of a comparator arm in either study, the sponsor has provided historical controls with these consisting of small studies of single agent therapies. See Table 91 from the Clinical Overview below.

Table 91. Treatment of relapsed or refractory Hodgkin lymphoma, after ASCT, prospective studies within the past 15 years

Agent(s)	Pub Date	Target Population	No. Treated	Prior ASCT	ORR (%)	CR (%)	PFS	DOR	Overall Survival
Brentuximab vedotin[24]	2012	Relapsed Refractory after ASCT	102	102	75%	34%	6 Month PFS: ~45% 1 Year PFS: ~35%	6.7 months	6 Month OS: ~95% 1 Year OS:89%
Panobinostat[25]	2012	Relapsed Refractory after ASCT	129	129	27%	4%	6 Month PFS: ~ 60% 1 Year PFS: ~ 40%	6.7 months (median)	6 Month OS: ~90% 1 Year OS: 78%
Everolimus[26]	2010	Relapsed Refractory HL	19	16	47%	5%	6 Month PFS: ~ 50% 1 Year PFS: ~ 26%	7.1 months (median)	6 Month OS: ~85% 1 Year OS: ~75%
Bortezomib[27]	2006	Relapsed Refractory HL with 2 prior regimens including stem cell transplant	14	13	7%	0	NS	NS	NS
Gemcitabine[28]	2004	Relapsed of chemo-refractory HL; received ≥ 2 prior different chemo regimens	27	16	22%	0	1 Year PFS: 24%	NS	1 Year OS: 64% 2 Year OS: 55%
Rituximab[29]	2003	Recurrent cHL with minimum 2 prior treatment regimens	22	18	22%	5%	NS	7.8 months (median)	NS

Abbreviations: ASCT = autologous stem cell transplant; cHL = classical Hodgkin lymphoma; CR = complete response; DOR = duration of response; HL = Hodgkin lymphoma; NS = not stated; ORR = objective response rate; OS = overall survival; PFS = progression free survival.
Note: Approximate (~) indicates estimation from Kaplan-Meier curve.

Nivolumab compares favourably to these agents (except for brentuximab vedotin) in terms of the ORR, although the median DOR of 10 to 12 months with nivolumab is only 3 to 4 months longer than those reported with the other agents. However, the sponsor's presentation of historical controls does not include other treatment options available to patients in this setting with these including combination chemotherapy, radiation and allo-SCT (see also the NCCN and ESMO guidelines and Section 2.1. Clinical rationale: Background above. Could the sponsor provide a more comprehensive description of the clinical relevance of nivolumab in the proposed setting, with this taking into account other treatment options available to these patients?

1.1.2.1. Sponsor's response

The sponsor's response noted that the NCCN and ESMO guidelines describe a variety of options or patients who have progressed after both ASCT and brentuximab. Include radiation, single-agent chemotherapy, combination chemotherapy, and agents with novel mechanism of actions. The sponsor states that '*none of these options are approved for this setting*' and published data on the activity of these options are very limited.

The sponsor provided an updated summary (shown in Table 92, below) of the use of agents reported in prospective studies over 15 years and including bendamustine, GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin) and lenalidomide in addition to the agents already shown in Table 91 above.

Table 92. An update on treatment of relapsed or refractory Hodgkin lymphoma, after ASCT: prospective studies within the past 15 years

Agent(s)	Pub Date	Target Population	No. Treated	Prior ASCT	ORR (%)	CR (%)	PFS	DOR	Overall Survival
Bendamustine[7] e	2013	Relapsed Refractory HL (median lines of prior therapy=4)	34	27	56%	35%	5.2 months (median)	5 months (median)	NS
Brentuximab vedotin[8]	2012	Relapsed Refractory after ASCT	102	102	75%	34%	6 Month PFS: ~45% 1 Year PFS: ~35%	6.7 months (median)	6 Month OS: ~95% 1 Year OS:89%
Panobinostat[9]	2012	Relapsed Refractory after ASCT	129	129	27%	4%	6 Month PFS: ~ 60% 1 Year PFS: ~ 40%	6.7 months (median)	6 Month OS: ~90% 1 Year OS: 78%
Lenalidomide[10]	2011	Relapsed Refractory HL	36	31	19%	3%	4 months (median)	6 months	20 months (median)
Everolimus[11]	2010	Relapsed Refractory HL	19	16	47%	5%	6 Month PFS: ~ 50% 1 Year PFS: ~ 26%	7.1 months (median)	6 Month OS: ~85% 1 Year OS: ~75%
GVD[12]	2007	Relapsed Refractory HL	91	36	75%	17%	EFS: 8.5 months 4 Year PFS: ~10% (36 subjects)	NS	4 Year OS: 34%
Bortezomib[13]	2006	Relapsed Refractory HL with 2 prior regimens including stem cell transplant	14	13	7%	0	NS	NS	NS
Gemcitabine[14]	2004	Relapsed of chemo-refractory HL; received ≥ 2 prior different chemo regimens	27	16	22%	0	1 Year PFS: 24%	NS	1 Year OS: 64% 2 Year OS: 55%
Rituximab[15]	2003	Recurrent cHL with minimum 2 prior treatment regimens	22	18	22%	5%	NS	7.8 months (median)	NS

Abbreviations: ASCT = autologous stem cell transplant; cHL = classical Hodgkin lymphoma; CR = complete response; DOR = duration of response; EFS = event-free survival; GVD = gemcitabine, vinorelbine, and pegylated liposomal doxorubicin; HL = Hodgkin lymphoma; NS = not stated; ORR = objective response rate; OS = overall survival; PFS = progression free survival.

Note: Approximate (~) indicates estimation from Kaplan-Meier curve.

The sponsor noted that, except for brentuximab, most agents used as monotherapy achieved a modest ORR and limited data on DOR and PFS indicate short durability of response.

The sponsor noted that data on the use of combination chemotherapy in the post-ASCT setting is very limited, with most studies including fewer than 10 patients. The use of GVD in this setting was referred to (see Table 92, above) as an example of the response that could be seen: high ORR but relatively short event-free survival. The sponsor considered that combination regimens are recommended only in specific circumstances (that is, to achieve best disease control prior to allo-SCT) due to high rates of Grade 3 or 4 myelosuppression.

The use of allo-SCT was described as only being offered only to patients who have achieved good disease control (at least PR) from salvage therapy. No further discussion of the use of allo-SCT was provided except for reference to a study of the efficacy and safety for subsequent SCT after nivolumab monotherapy ClinicalTrials.gov identifier: NCT02098512).

The use of radiation therapy was descried as only used for localised disease. It was thought to be unlikely to be of benefit to the target population due to most of these patients having extensive disease (Stage III to IV). The sponsor noted that only 1 of the 95 subjects from Cohort B and Study CA209039 ASCT-Bren Failed group had Stage 1 disease.

The sponsor concluded that, '*In this post-ASCT/post-brentuximab setting, while the ORR with certain historical controls (for example, GVD) can be comparable to nivolumab, the durability of response consistently favors nivolumab (median DOR = 13.1 months; median PFS = 14.9 months; 12-month PFS rate = 55%;* [see the response to Question 16, above] *over historical controls*.'

11.4.10.1. Evaluator's response

The evaluator acknowledges that data in this area is extremely limited. However, in the absence of a control arm in either of the studies provided to support the proposed indication, comprehensive comparison to historical data and current clinical practices is essential. The evaluator agrees that the OR reported with nivolumab in patients with r/r cHL is comparable to that reported with alternative treatment options. The updated efficacy results provided in response to Question 16 indicate a duration of response of 13.1 months (compared to

7.8 months in the analysis provided in the interim CSR). This compares favourably to the treatment options presented in the sponsor's table.

11.5. Safety

11.5.1. Question 26: Updated safety analysis of adverse events

The sponsor's assessment of safety is based on the interim results from 2 small exploratory Phase I and Phase II studies. In the Phase I study of 23 patients (15 of whom match the proposed target population), the median duration of follow-up was 23 months and most patients had discontinued treatment at the time of database lock for the interim analysis. In the Phase II study, patients were recruited in three cohorts, only one of which matches the proposed target population. Enrolment into the different cohorts was staggered with this resulting in considerably lower nivolumab exposure and duration of follow-up in Cohort C and Cohort A compared to Cohort B and compared to Study CA209039. The median duration of study therapy was not reached at the time of the interim analysis for any cohort in Study CA209205; the median duration of therapy in CA209039 was 8.2 months. The median number of doses received at the time of the interim analysis was 18 for Study CA209039, 17 for Cohort B, 11 for Cohort A and 6 for Cohort C.

Each cohort in Study CA209205 had relatively brief duration of follow-up and most patients were still receiving nivolumab treatment. Due to the relatively brief follow-up, safety results for this study may be considered 'immature'. The evaluator notes that the sponsor has acknowledged this in the SCS with the statement: '*Compared with CA209205 Cohort B and CA209039 all cHL, the safety profile for subjects in CA209205 Cohort A or Cohort C may not be as adequately characterized at these database locks due to the shorter extent of follow up in these cohorts.'*

The evaluator notes that database lock for the interim analysis for Study CA209205 was August 2015. A safety analysis that includes an additional 6 or 12 months of observations from this study would be far more generalisable to the proposed population and would provide more stable rates of events for comparison to other tumour types.

The evaluator requests that an updated analysis of safety for Study CA209205 be provided. This should include:

- Nivolumab exposure – median (min, max) number of doses, cumulative dose, estimated median duration of treatment for Cohorts A, B and C of CA209205
- Updated Adverse Event data using the format of the SCS Tables and with the display columns of the integrated SCE population, and the integrated cHL population
  - Table 'Summary of Safety'
  - Table 'Summary of Any Adverse Events by Worst CTC Grade Reported within 30 Days of Last Dose in ≥ 5% of Treated Subjects'
  - Listing of Adverse events leading to dose delay
  - Table 'Death Summary (and including narrative summaries of any deaths due to study drug toxicity or other)'
  - Table 'Summary of SAEs (All Causality) by Worst CTC Grade Reported within 30 Days of Last Dose in ≥ 1% of Subjects'
  - Table 'Summary of AEs Leading to Discontinuation (All Causality) by Worst CTC Grade Reported within 30 Days of Last Dose'
  - Table 'Summary of Select AEs Reported Up to 30 Days After Last Dose'

This data should also be used for the display of AEs reported in cHL patients and for the display of rates of select AEs in the pooled population in the PI. Any other data that is regarded as informative by the sponsor may also be included.

11.5.1.1. Sponsor's response

The sponsor acknowledged there were considerably lower nivolumab exposure and duration of follow-up in Cohorts A and Cohort C compared with Cohort B in Study CA209039 at the time of the interim analysis with data included in the CSRs with the original submission. In the response, the sponsor provides updated the safety data from Study CA209205 from the most recent DBL (June 2016 DBL). In this presentation, the median number of doses received had increased from 11 and 6 (October 2015 DBL) to 25 and 21 (June 2016 DBL) and the median durations of follow up had increased from 5.09 and 2.83 months (October 2015 DBL) to 14.00 and 10.64 months (June 2016 DBL) in Cohorts A and C, respectively.

The updated tables were provided in Appendices to the response. No analysis of these tables was provided other than:

'With the mature data with longer follow-up, nivolumab monotherapy has an acceptable safety profile in heavily pre-treated subjects with cHL. Overall, the safety profile of nivolumab in Cohort A + B + C was consistent with prior data from previous nivolumab monotherapy studies in terms of type, frequency, and severity of AEs. No new safety concerns with nivolumab monotherapy treatment were identified compared with those reported in studies of patients with solid tumours. As of the 28 June 2016 DBL, there were no treatment related deaths.'

11.5.1.2. Evaluator's response

The duration of follow-up for safety for each cohort of Study CA209205 was provided in the response to a separate question.

Table 93. Extent of follow-up for safety analysis

TIME BETWEEN DATE OF FIRST DOSE DATE AND LAST KNOWN DATE ALIVE (FOR SUBJECTS WHO ARE ALIVE) OR DEATH (MONTHS)

	Cohort A N = 63	Cohort B N = 80	Cohort C N = 100	Cohort A+B+C N = 243
MEAN	13.32	15.90	10.56	13.03
MEDIAN	14.00	17.00	10.64	12.85
MIN, MAX	1.0, 20.3	1.9, 21.9	1.4, 15.3	1.0, 21.9
STANDARD DEVIATION	3.845	4.349	2.763	4.285

Source: Refer to Interim 02 CSR for CA209205; Table S.5.15 (from June DBL)

The tables related to adverse events were presented as:

1. the combined results for the three cohorts of Study CA209205 and the separate results for Cohort B of Study CA209205.
2. the results for the SCE group (Cohort B + the ASCT-Bren failed group).

These tables have been compared to the equivalent tables in the Summary of Clinical Safety (SCS) provided in the submission and to sections of the Clinical Safety section above. A tabulated summary of safety is provided below in Table 94.

Table 94. Summary of Safety: June 2016 DBL and February 2016 DBL

	All cHL (Cohort A + B + C of CA209205 and CA209039) June 2016 DBL	**SCE population June 2016**	**All cHL (Cohort A, + B + C of CA209205 and CA209039) Feb 2016 DBL**
	N = 266	N = 95	N = 263

	All cHL (Cohort A + B + C of CA209205 and CA209039) June 2016 DBL	SCE population June 2016	All cHL (Cohort A, + B + C of CA209205 and CA209039) Feb 2016 DBL
Median duration of therapy (months), (range)	18.63 (0 to 23.4)	13.8 (1.1 to 23.4)	NA
Total subjects with an event (%)			
All Cause, all grade AEs	263 (98.9)	95 (100)	246 (93.5)
All Cause, Grade 3 or 4 AEs	100 (37.6)	47 (49.5)	79 (30)
Drug-related AEs, Grade 3 or 4	56 (21.1)	27 (28.4)	42 (16.0)
Discontinuations due to AEs	19 (7.1)	7 (7.4)	11 (4.2)
SAEs, all grades, all causality	68 (25.6)	29 (30.5)	55 (20.9)
Deaths	23 (8.6)	11 (11.6)	12 (4.6)
Within 30 days of last dose	6 (2.3)	2 (2.1)	4 (1.6)
Within 100 days of last dose	9 (3.4)	1 (1.1)	5 (1.9)
Attributed to nivolumab toxicity	0	0	1* (0.4)
In the 1 March 2016 SCS, 1 death was previously attributed to study drug toxicity: a Grade 5 SAE of atypical pneumonia considered related to study treatment by the investigator was changed by the investigator to unrelated post database lock in one patient. See also Section 8 'Deaths in Study CA209205' above.			

For the SCE population (Cohort B of CA209205 and the ASCT-Bren Failed group in Study CA209039; n = 95):

- All grade and all cause AEs were reported in 100% of patients. The most common of these (reported in > 25% of patients) were fatigue (40%), cough (39%), pyrexia (38%), diarrhoea (38%), upper respiratory tract infection (28%), rash (27%), pruritus (26%) and arthralgia (25%).
- Grade 3 or 4 adverse events, all cause, were reported in 49.5% of patients. Grade 3 or 4 AEs reported in two or more patients were: lipase increased (8.4%), decreased neutrophil count (3.2%), AST increased (3.2%), neutropaenia (4.2%), ALT increased, amylase increased, anaemia, pneumonia, upper respiratory tract infection, dyspnoea, lung infection, rash, skin infection, abdominal pain, autoimmune hepatitis (2 patients each, 2.1%).
- SAEs, all cause and all grade, were reported in 30.5%, with Grade 3 or 4 in 20%. Grade 3 or 4 SAEs, all cause, were all reported in single patients and included: pneumonia, lung infection, dyspnoea, meningitis, pyrexia, generalised oedema, arrhythmia, pericardial effusion, cardiac failure, gastrointestinal stromal tumour, hypercalcaemia, syncope, rash, maculopapular rash, platelet count decreased, osteonecrosis, febrile neutropaenia and embolism.
- Discontinuations due to AEs in 7 patients (7.4%).

With the longer period of follow-up for the three cohorts of Study CA209205, a total of 23 deaths had been reported (compared to 12 at the previous analysis). The number and proportion of patients in whom SAEs were reported or who had discontinued study treatment due to AEs had also increased. There were no Grade 5 AEs that had not been reported at the earlier time point.

The ordering of the most frequently reported AEs was roughly the same for each group and timepoint. The list of AEs shown in the presentation of AEs, all cause, and Drug-related AEs, according to 5% cut-off, was similar at the two time points. The pattern of Grade 3 or 4 events was also similar. The overall rate of each AE in the tables had, in general, increased, for example the reported rate of fatigue in the SCS in Cohort B was 36.3% compared to 40% in the June 2016 analysis; the reported rate of rash in the SCS in Cohort B was 21.3 % compared to 25.0 % in the June 2016 analysis.

Of the 23 deaths, 13 were reported to be due to disease progression and 'unknown' in 10. Of the 6 who died within 30 days of last dose, the cause of death was reported to be disease progression in 3 and unknown in 3. Of the 9 who died within 100 days of last dose, the cause of death was reported to be disease progression in 5 and unknown in 4. Narratives of deaths reported for 'other causes' were provided. Those deaths that have not been described above in Section 8 'Clinical Safety' are described here:

- One subject discontinued nivolumab due to pneumonitis. This was reported to resolve. The patient died some 60 days later from MOF; no further details were provided.
- One subject developed hypercalcaemia on Day 70 of treatment and was treated with pamidronate and calcitonin. The patient was pyrexial on Day 113 and study treatment was discontinued (last dose given on Day 99). On Day 124, the pyrexia was reported to resolve but on the same day the patient hospitalised with acute respiratory distress syndrome. The patient died from a cardiac arrest the next day. The acute respiratory distress syndrome, and subsequent cardiac arrest, does not appear to have been considered as related to study treatment.
- One subject was discontinued from study therapy on Day 212 in preparation for an allogenic stem cell transplant, which was performed on Day 233. On Day 267 (20 January 2016), 55 days after the (last) infusion 16, the subject required admission to an intensive care unit with Grade 4 graft versus host disease. He received unspecified treatment for this event. On Day 272 (25 January 2016), the subject died of graft versus host disease.
- One subject discontinued treatment on Day 64 due to persistent dizziness, with the last dose administered on Day 29. The patient subsequently was treated with brentuximab vedotin. On Day 160, the patient was hospitalised with hyperglycaemia that was considered an endocrine IMAE related to nivolumab. On Day 264, the patient was reported to have died from pneumonia.

On the information provided it is not possible to exclude a contribution of immune related AEs secondary to nivolumab to the deaths of the first three of these patients.

The pattern of reported SAEs appeared similar at the two time points, with no new Grade 5 events. Drug-related SAEs were reported in an additional 3 subjects and an additional 6 patients discontinued due to AEs. Comparison of the tables (as presented) did not allow for identification of the SAEs or AEs that led to discontinuation in these patients.

Overall, the rate and type of AEs with longer follow-up was similar in Cohorts A and C to that reported in the SCE and in Cohort B. There were no new safety signals identified.

11.5.2. Question 27: Updated comparison across tumour types

As noted above, enrolment into the different cohorts of Study CA209205 was staggered with this resulting in considerably lower nivolumab exposure and duration of follow-up in Cohort C and Cohort A compared to Cohort B and compared to Study CA209039. As the sponsor states in the SCS, '*Compared with CA209205 Cohort B and CA209039 all cHL, the safety profile for patients in CA209205 Cohort A or Cohort C may not be as adequately characterized at these database locks due to the shorter extent of follow up in these cohorts.'* The median duration of study therapy was not reached at the time of the interim analysis for any cohort in Study CA209205; the median duration of therapy in Study CA209039 was 8.2 months. The median number of doses received

at the time of the interim analysis was 18 for Study CA209039, 17 for Cohort B, 11 for Cohort A and 6 for Cohort C.

Given that the occurrence of AEs appears to be related to exposure, the evaluator is concerned that inclusion of Cohort A + C, which numerically makes up 160/240 (67%) of the study population of Study CA209205, and 160/263 (61%) of the integrated cHL population, has diluted the safety results. This may cause under-estimation of AEs and overestimation of safety for the proposed population. The sponsor is asked to provide a comparison across tumour types using both the integrated SCE and the integrated cHL populations, with this comparison based on the format used in 3 SCS tables [not included here], to enable comparison of the frequency of AEs in the target population to that of other tumour types? These tables should include updated data that is available from Studies CA209039 and CA209205.

11.5.2.1. Sponsor's response

The sponsor provided several tables containing updated data for Study CA209205 based on the most recent database lock (DBL), June 2016 and safety related data for other tumour types. A comparison of nivolumab exposure according to duration of treatment and number of doses was also provided. From these tables, the sponsor concluded that the longer follow-up data in subjects with cHL are consistent with those observed in subjects with solid tumours.

11.5.2.2. Evaluator's response

The data provided across several tables in the sponsor's response has been collated in Table 95 below to facilitate comparison. From the data, it is apparent that the cHL population received nivolumab for considerably longer than the patients with solid tumours. However, even with the longer follow-up, there still appear to be differences between the cHL SCE population (the target population for the proposed indication) and the cHL SCS population (the total cHL population).

Table 95. Updated comparison of cHL populations (June 2016 DBL) to other tumour types

	cHL SCS population[a]	cHL SCE population[b]	RCC	Melanoma	NSCLC
	N = 266	N = 95	N = 406	N = 787	N = 535
Median duration of therapy (months)	18.6	13.84	5.5	5.8	2.7
Total subjects with an event (%)					
All Cause, all grades AEs	263 (98.9)	95 (100)	397 (97.8)	768 (97.6)	524(97.9)
All cause, Grade 3 or 4 AEs	100 (37.6)	47 (49.5)	216 (53.2)	319 (40.5)	244 (45.6)
Drug-related AEs, all grade	207 (77.8)	86 (90.5)	319 (78.6)	609 (77.4)	362 (67.7)
Drug-related AEs, Grade 3 or 4	56 (21.1)	27 (28.4)	76 (18.7)	108 (13.7)	59 (11.0)
Discontinuations due to AEs	19 (7.1)	7 (7.4)	72 (17.7)	91 (11.6)	99 (18.5)
SAEs, all grades	68 (25.6)	29 (30.5)	194 (47.8)	319 (40.5)	263 (49.2)
SAEs, drug related	29 (10.9)	27 (28.4)	76 (18.7)	108 (13.7)	69 (11.0)
Deaths	23 (8.6)	11 (11.6)	181 (44.6)	251 (31.9)	339 (63.4)

	cHL SCS population[a]	cHL SCE population[b]	RCC	Melanoma	NSCLC
Within 30 days of last dose	6 (2.3)	2 (2.1)	19 (4.7)	57 (7.2)	66 (12.3)
Within 100 days of last dose	9 (3.4)	2(2.1)	56 (13.8)	151 (19.2)	181 (33.8)
Attributed to nivolumab toxicity	0[c]	0[c]	0	1 (0.1)	2 (0.4)
Most frequently reported AEs, all grades					
Fatigue	90 (33.8)	38 (40.0)	195 (49.0)	328 (41.7)	189 (35.3)
Pyrexia	76 (28.6)	36 (37.9)	67 (16.5)	114 (14.5)	76 (14.2)
Diarrhoea	87 (32.7)	36 (37.9)	96 (23.6)	223 (28.3)	86 (16.1)
Cough	88 (33.1)	37 (38.9)	120 (31.5)	148 (18.0)	154 (28.0)
Nausea	54 (20.3)	22 (23.2)	115 (28.3)	213 (27.1)	117 (21.9)
Pruritus	53 (19.9)	25 (26.3)	75 (18.5)	182 (23.1)	56 (10.5)
Rash	52 (19.5)	26 (27.4)	64 (15.8)	176 (22.4)	60 (11.2)

a) cHL SCS population = Cohorts A, B and C of Study CA209205 + Study CA209039; b) cHL SCE population = Cohort B of Study CA209205 + ASCT-Bren Failed group from Study CA209039; c) In the 1 March 2016 SCS, 1 death was previously attributed to study drug toxicity: a Grade 5 SAE of atypical pneumonia considered related to study treatment by the investigator was changed by the investigator to unrelated post database lock. d) the median duration of therapy was not reached for Cohort B and was 12.09 months for the sub-group of Study CA209039. RCC = renal cell carcinoma; NSCLC = non-small cell lung carcinoma.

The cHL SCE population had higher rates of Grade 3 or 4 AEs, drug related AEs (all grade and Grade 3 or 4) and SAEs (all cause and drug related) compared to the cHL SCS population and higher rates of drug related AEs (all grade and Grade 3 or 4) and drug related SAEs compared to solid tumour types. Despite this, the rate of discontinuation due to AEs was similar in both cHL populations and lower than that reported with solid tumour types.

These discrepancies between the two cHL populations may reflect the small numbers of patients with cHL who have received treatment with nivolumab in the clinical studies provided. The discrepancies limit any conclusions that may be drawn regarding the safety of nivolumab in patients with cHL compared to patients with solid tumours. The safety of nivolumab in patients with cHL has yet to be fully characterised and the possibility that more frequent drug-related AEs and SAEs may occur in these patients (compared to patients with other tumour types) cannot be excluded. Potential contributors to such an increase include the longer duration of therapy observed and the increased exposure per dose to nivolumab seen in cHL patients.

11.5.3. Question 28: Reporting of AEs in Study CA209205

According to the study protocol, AEs were to be collected for up to 100 days post-last dose of nivolumab and AEs were to be collected '*continuously*' throughout the study. The last follow-up visit was to occur at 80 days (± 7) after the last dose. Could the sponsor describe how information regarding AEs was to be collected 'continuously' during the study as the evaluator was unable to locate a description of this in the study protocol or interim CSR?

11.5.3.1. Sponsor's response

The sponsor clarified the timing of the follow-up visits in Study CA209205. Apparently the first visit 35 days (± 7 days) after the last dose and the second visit occurred at 80 days (± 7 days) from the first visit and not 80 days from the last dose.

11.5.3.2. Evaluator's response

The actual method by which information regarding AEs was to be collected 'continuously' was not described by the sponsor.

11.5.4. Question 29: Discontinuations due to nivolumab toxicity in StudyCA209205

According to a table [not included here] of the interim CSR, there were 4 patients in Cohort B who discontinued nivolumab treatment due to nivolumab toxicity. According to the interim CSR there were 3 patients in Cohort B who discontinued nivolumab treatment due to all cause AEs. Could the sponsor please explain this discrepancy?

11.5.4.1. Sponsor's response

According to the sponsor's response, the table showed only those patients in whom adverse events leading to discontinuation which were reported between first dose and 30 days after last dose of study therapy, whereas the table [in the question above] did not have this time limitation. There was one patient who experienced Grade 2 pneumonitis with onset of the event 35 days after the last dose of nivolumab. This patient was included in the first but not in the second table.

11.5.4.2. Evaluator's response

The sponsor's response is noted.

11.5.5. Question 30: Terminology and immune-mediated AEs

A number of terms are used by the sponsor in the different documents to describe AEs that may be immune mediated:

- The CSR for Study CA209205 uses the terms 'Select Adverse Events', 'Immune-mediated adverse events' and 'other events of special interest'.
- The CSR for Study CA209039 uses the terms 'Select Adverse Events', 'Immune-mediated adverse events' and 'other IMAEs of special interest' to describe AEs that may be immune mediated.
- The SCS uses the terms 'Select Adverse Events' and 'other events of special interest'.
- The PI uses the terms 'immune-related adverse reactions' and 'selected adverse reactions'.

From the definitions provided, all of these terms describe AEs that are considered by the sponsor to potentially be immune mediated, although different reporting periods, different composite PTs and different requirements for immunosuppressive therapy are used across these terms. The definitions and time frames appear to be arbitrarily determined. The evaluator is concerned that the use of multiple different terms adds unnecessary complexity to the descriptions of these AEs, risks obscuring the likely immune basis and makes determining the frequency of individual AE types difficult. If the term Immune Mediated Adverse Reactions or Events was used for all of these AEs, the frequency of occurrence would be clearer, it would also be more evident that these present across a spectrum of severity and that they may, or may not, require immunosuppression. As an example of the possible resulting confusion, the evaluator notes that due to the different terms used in the CSRs, pancreatitis in a patient in Study CA209039 was not considered an OESI (as treatment with corticosteroids was not administered) whereas a patient with pancreatitis in CA209205 would be reported as an OESI.

Could the sponsor provide a rationale for the terminology that has been chosen by the sponsor and, in particular, why the distinction is made between IMAEs and select AEs?

The evaluator recommends that these AEs be more simply referred to as immune mediated AEs, with this including select AEs with a reporting period of 100 days and OESIs. Could the sponsor please comment?

11.5.5.1. Sponsor's response

According to the sponsor's response, some of the differing definitions have resulted from advice from regulatory bodies. The sponsor had intended to use the term 'Select AE' for adverse events with a potential immune mediated aetiology based on the original criteria. Following advice from the FDA that events should be included regardless of investigator-assessed causality and for the time period of 100 days after last dose but limited to events (other than endocrine events) requiring immunosuppression, the sponsor introduced the term (IMAEs) to differentiate from the original methodology accepted in the EU.

Descriptions of Select AEs and IMAEs as provided in the documents in the dossier were again provided.

11.5.5.2. Evaluator's response

The evaluator is of the opinion that as a better understanding of the nature of immune-related events secondary to nivolumab develops, it is appropriate to re-think the terminology and definitions used. The evaluator is also of the opinion that hypersensitivity/infusion reactions should be considered another type of immune related AE.

11.5.6. Question 31: Descriptions of select AEs and OESIs

The evaluator notes that the presentation of AEs that may be immune mediated in the SCS is limited to select AEs (with a reporting period of 30 days) and to OESIs. IMAES, with the longer reporting period of 100 days, are described in the individual interim CSRs. The evaluator has a number of concerns regarding this presentation:

- The populations presented in the descriptions are the integrated cHL population and Cohort B from Study CA209205. The integrated SCE population, that represent the target population for the indication, has not been presented.
- The more detailed summaries of each of the categories of select AEs in the SCS (including grades, time to onset, time to resolution, treatment with immune-suppressive/immunomodulatory medications, outcome) is further limited to those AEs considered to be drug related by the investigators. This assessment is subjective and dependent on the investigator's training and recognition of immune mediated AEs. Comparison of the attribution of treatment related or not for the two studies shows considerable differences (see also Question 32, below) and this raises concerns that limiting the descriptions to 'drug related' AEs can underestimate the true frequency, although the evaluator recognises that some of the reported events may be caused by cHL or other concomitant comorbidities.
- The inclusion of patients from Cohort A and C is appropriate for the identification of rarer select AEs/OESIs in the cHL population. However, this inclusion has rendered the detailed summaries of each of the categories of select AEs in the SCS difficult to interpret, given that many of these Cohort C and A patients have had insufficient time to determine the outcome of the AE and the effect of re-exposure.

The sponsor is asked to provide a revised presentation of AEs that may have an immune basis (select AEs and OESIs) using updated data from both studies. The presentation should be of the integrated SCE population and the integrated cHL population. The reporting period of select AEs should be 100 days and the summaries for each category (including grades, time to onset, time to resolution, treatment with immune-suppressive/immunomodulatory medications, outcome of the event, effect of re-exposure) should be for all causality AEs.

11.5.6.1. Sponsor's response

As with the responses to earlier questions, the sponsor acknowledged '*that subjects in Cohorts A and C of CA209205 did not have sufficient follow-up duration to appropriately evaluate safety, including select AEs/OESIs in the cHL population at the time of October 2015 DBL*'. A description of the relative median duration of exposure for the different cohorts of Study CA209205 was provided: '*The median durations of follow up were prolonged from 5.09 and 2.83 months (October 2015 DBL) to 14.00 and 10.64 months (June 2016 DBL) in Cohorts A and C, respectively*'. A table of links to 20 different appendices and tables was provided. The sponsor stated that: '*Based on the more mature safety data from Cohorts A and C, the frequencies of select AEs with extended follow-up and OESIs appeared consistent between the SCE Population (n = 95) and the Integrated cHL SCS Population (n = 266).'*

11.5.6.2. Evaluator's response

The evaluator requested a revised presentation of immune related AEs. The sponsor has responded by providing over 100 pages of source data with no analysis or integration of the data. Table 96 below has been constructed by the evaluator. The conclusion drawn by the sponsor is difficult to substantiate; in general the rates reported in the SCS population are lower than those in the SCE population. It is not clear as to whether the SCE population is different from the SCS population or if this is the effect of small numbers.

Table 96. Updated comparison of immune related AEs in the cHL populations

	cHL SCE population[2] **N = 95**	cHL SCS population[1] **N = 266**
Total subjects with an event (%)		
Select AE (100 days)	38 (40)	93 (35)
Select AE, Grade 3 or 4	2 (2.1)	8 (3.0)
Discontinuations due to select AEs	1 (1.1)	2 (0.8)
Select AEs by category and use of immunosuppressive therapy		
Number of patients who experienced at least one event in each category[3]	154	360
Number of patients who received immunosuppressive therapy according to category of select AE	41[4] (43.2)	76 (28.6)
Select AE categories		
Number resolved/number with an event (%)		
'Skin adverse event'	36/42 (85.7)	76/94 (80.9)
'Gastrointestinal adverse event'	32/35 (91.4)	85/89 (95.5)
'Hypersensitivity/infusion reaction'	18/20 (90.0)	42/46 (91.3)
'Endocrine adverse event'	10/19 (52.6)	21/46 (45.7)

	cHL SCE population[2] **N = 95**	cHL SCS population[1] **N = 266**
'Hepatic adverse event'	13/17 (76.5)	28/42 (66.7)
'Pulmonary adverse event'	6/7 (85.7)	17/18 (94.4)
'Renal adverse event'	3/9 (33.3)	6/15 (40.0)
Number of patients who received immunosuppressive therapy/total number of patients with an event (%) for categories of select AE		
'Skin adverse event'	22/44 (50)	34/99 (34.3)
'Gastrointestinal adverse event'	1/38 (2.6)	6/93 (6.5)
'Hypersensitivity/infusion reaction'	6/20 (30.0)	12/46 (26.1)
'Endocrine adverse event'	2/19 (10.5)	2/46 (4.3)
'Hepatic adverse event'	5/17 (29.4)	12/43 (27.9)
'Pulmonary adverse event'	5/7 (71.4)	14/18 (77.8)
'Renal adverse event'	0/9	1/15 (6.7)
Other events of special interest		
Patient number		
Pancreatitis	2	3
Uveitis	1	2
Iritis	0	1
Encephalitis	0	2
Myasthenic syndrome, Guillain-Barre syndrome	0	0
1) cHL SCS population = Cohorts A, B and C of Study CA209205 + Study CA209039; 2) cHL SCE population = Cohort B of Study CA209205 + ASCT-Bren Failed group from Study CA209039; 3)patients could experience events from more than one category; 4) patients could have immunosuppressive treatment for events from more than one category. According to the sponsor's response to Question 15, there were 26 patients in the SCE who received immunosuppressive treatment.		

11.5.7. Question 32: Select AEs drug related or not; the investigators of Study CA209205 and CA209039

Many of the AEs described as select AEs or IMAEs or OESIs have non-specific presentations. As a result, the assessment of these AEs as possibly being drug related is dependent on the investigator's understanding and recognition of this new class of adverse effects. There is a

difference in the attribution of select AEs as drug-related or not in the two studies presented in the dossier:

- Among patients treated with nivolumab in all cohorts of Study CA209205 (263 patients), there were 215 select AEs reported. The interim CSR states that '*The majority of select AEs reported were Grade 1 or 2, and most were considered drug-related by the investigator*.'
- In Study CA209039, there were 52 reports of select AEs among the 23 cHL patients treated with nivolumab. The interim CSR states that '*The majority of Select AEs reported was Grade 1 or 2 and were considered not drug-related by the investigator*'.

Comparison of rates of categories of select AEs considered drug-related versus not drug related in the two CSRs confirms these statements.

The sponsor is asked to comment on why most select AEs were considered drug related by the investigators of Study CA209205 but were not considered drug related by the investigators of Study CA209039, with this including a description of the training provided to the investigators in each study regarding the recognition and management of AEs that are potentially immune mediated.

11.5.7.1. Sponsor's response

In the sponsor's opinion, the reason that majority of select AEs were reported as non-drug related in Study CA209039 was incidental due to limited number of the treated subjects and subjects experiencing select AEs in the Phase I Study. The following tabulated summary was provided, shown below in Table 97.

Table 97. Summary of selected adverse events reported up to 100 days after last dose, all nivolumab treated subjects

	CA209205 Cohort A+B+C N = 243			CA209039 N = 23		
Select AE Category (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ENDOCRINE						
ALL-CAUSALITY	41 (16.8)	1 (0.4)	0	5 (21.7)	0	0
DRUG-RELATED	31 (12.8)	0	0	3 (13.0)	0	0
GASTROINTESTINAL						
ALL-CAUSALITY	82 (33.7)	6 (2.5)	0	11 (47.8)	2 (8.7)	0
DRUG-RELATED	38 (15.6)	5 (2.1)	0	4 (17.4)	1 (4.3)	0
HEPATIC						
ALL-CAUSALITY	34 (14.0)	14 (5.7)	0	9 (39.1)	1 (4.3)	0
DRUG-RELATED	26 (10.7)	11 (4.5)	0	2 (8.7)	0	0
PULMONARY						
ALL-CAUSALITY	15 (6.2)	2 (0.8)	0	3 (13.0)	1 (4.3)	0
DRUG-RELATED	14 (5.8)	1 (0.4)	0	1 (4.3)	1 (4.3)	0
RENAL						
ALL-CAUSALITY	13 (5.3)	3 (1.2)	0	2 (8.7)	1 (4.3)	0
DRUG-RELATED	5 (2.1)	1 (0.4)	0	0	0	0
SKIN						
ALL-CAUSALITY	85 (35.0)	4 (1.5)	0	14 (60.9)	0	0
DRUG-RELATED	51 (21.0)	0	0	5 (8.7)	0	0
HYPERSENSITIVITY/INFUSION REACTION						
ALL-CAUSALITY	42 (17.3)	2 (0.8)	0	4 (17.4)	0	0
DRUG-RELATED	39 (16.0)	2 (0.8)	0	2 (8.7)	0	0

MedDRA Version: 19.0

CTC Version 4.0

Includes events reported between first dose and 110 days after last dose of study therapy.

A description of the training and monitoring of clinical investigators on the recognition, monitoring, and treatment of AEs that are potentially immune-mediated with nivolumab use was provided. At the time of the investigator meetings, the investigator and study team were trained on the review/identification of irARs and the recommended treatment algorithm for each. Breakout sessions were organized to allow investigator to ask questions in small groups and discuss specific de-identified cases used as examples. All investigators were provided a copy of the algorithms and each was reviewed along with possible events, their treatment, and monitoring through resolution. The medical monitor(s) reviewed serious adverse event

notifications daily and followed up in real-time with investigators to ensure thorough diagnostic and appropriate management of these AEs. All SAEs and deaths are reviewed by the sponsor pharmacovigilance groups and the global clinical research group. Timely queries were generated and sent to sites when inconsistent attribution or treatment management were identified. Additional safety trainings were provided to sites in need by the local site monitors.

11.5.7.2. Evaluator's response

The evaluator does not agree that the occurrence of all cause select AEs in Study CA209039 was infrequent, given that there were 52 events reported for the 23 patients. It is also evident from the tabulated summary provided by the sponsor that there was a lower rate of attribution of these events as 'drug-related' in Study CA209039.

In terms of training and monitoring, the sponsor has described a robust process of monitoring for SAEs. There was no process of monitoring All grade select AEs or Grade 3 or 4 select AEs. Recognition of these events as drug-related was therefore dependent on investigator familiarity and training. It would appear that exposure to more patients, as occurred in Study CA209205, resulted in greater familiarity and recognition.

The importance of this is that with the introduction of nivolumab into wider use, there will be a 'learning curve' experienced by clinicians in the recognition of this new type of adverse reaction and the safety seen in clinical trials may not be replicated. However, the evaluator notes that, over the last 12 months there have been an increasing number of review articles and guidelines available to clinicians that address the issue of immune related AEs, for example, the recently releasing guidelines by eviQ.

11.5.8. Question 33: Patients with multiple select AEs

The SCS provides a table of the number of patients who experienced more than one event within the one category of select AEs [table not included here]. This shows that very few patients experience repeated events within the one category. From the narratives, however, it is evident that some patients experienced multiple events with these coming from more than one category and that this could have a significant impact on the patient's quality of life. Could the sponsor provide a summary of the patients who experienced select AEs from more than one of the categories used to describe select AEs and OESIs (including hypersensitivity events)? This should be shown for the populations of the integrated SCE population, Cohort B and the integrated cHL population and should show the total number of select AEs from all categories for each population and a frequency distribution of the number of select AEs from all categories per patient using the groupings of 1 event, 2 to 3 events, ≥ 4 events.

11.5.8.1. Sponsor's response

The sponsor clarified the counting algorithm in the multiple event table. To generate the unique event table, multiple occurrence of a preferred term within 1 category of select AEs (that is, 'diarrhoea' within 'gastrointestinal adverse event') 1 subject experienced were first collapsed if the events (that is 'diarrhoea') were overlapping or contiguous in time and only the non-overlapped events for a preferred term were counted as multiple events. As a result, the incidence of multiple events in the table could be lower than a simple counting method.

The sponsor was unable to provide a summary of the patients who experienced select AEs from more than one of the categories used to describe select AEs and OESIs (including hypersensitivity events) as '*collapsing across multiple categories would be difficult to interpret given the unique event table was summarised per preferred term*.'

11.5.8.2. Evaluator's response

It is disappointing that the number of different types of select AEs that may be experienced by patients could not be displayed in the sponsor's response as this would provide further insight into the impact of nivolumab therapy on patients. Some information was provided in response to a different question. In an appendix provided in response to Question 31, the number of

patients with a select AE is provided for each category of select AEs (see evaluator's summary table above). This number totalled 154 for the SCE population, suggesting that the 95 patients in the SCE group experienced select AEs from 1 or 2 categories, on average.

11.5.9. Question 34: Hypersensitivity/infusion related reaction category adverse events in cHL patients compared to other tumour types

The incidence rate of hypersensitivity/infusion related reactions was similar in both CA209039 and CA209205 (17.4% and 15% respectively). The Summary of Clinical Pharmacology presentation of provides a summary of select adverse events in the hypersensitivity/infusion reaction category by ADA Status (positive or negative) for all subjects who were treated with nivolumab monotherapy and in whom the ICDIM 140 ADA assay was used (Studies CA209063, CA209037, CA209066, CA209017, CA209057,CA209067, CA209025, CA209039 and CA209205). This showed an incidence of hypersensitivity/infusion reaction category events of 9.6% for the total pooled population (see Figure 32 Summary of nivolumab using ICDIM…). This is considerably lower than the rates reported in both Studies CA209039 and CA209205. The sponsor is asked to provide a comparison of the incidence rates hypersensitivity/infusion reaction category events for patients with other tumour types (melanoma, NSCLC, RCC) treated with nivolumab monotherapy and to provide comment if this shows a difference across tumour types.

11.5.9.1. Sponsor's response

The sponsor noted that among the most frequently reported drug-related AEs (≥ 10% of subjects), infusion related reactions were reported more frequently (> 5% difference) in cHL than in RCC, NSCLC, and melanoma. infusion-related reactions, which was reported more frequently in cHL (14.1%) compared with RCC (5.2%), melanoma (4.8%), and NSCLC (2.2%).

The sponsor re-iterated that the higher frequency of infusion related reactions in cHL could be attributed, in part, to a high incidence of infusion-related reactions that occurred at one Study CA209205 centre in Germany (15/30 treated subjects at the site had infusion related reactions), which accounted for 46.9% (15/32) of all infusion related reactions in Study CA209205.

11.5.9.2. Evaluator's response

The occurrence of infusion related reactions at this site in Germany is discussed further below.

11.5.10. Question 35: Defining infusion related reactions

The sponsor's SCS notes that '*a high incidence of infusion-related reactions that occurred at one CA209205 study center in Germany (15/30 treated patients at the site had infusion related reactions), which accounted for 46.9% (15/32) of all infusion-related reactions in CA209205. Consequently, the observed incidence of infusion reactions in CA209205 was higher in Europe (18.3%) than in US/Canada (7.0%)'.*

The evaluator was unable to locate a definition of 'infusion related reaction' in the study protocol and notes that this is defined as *'A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances*' in the National Cancer Institute Common Toxicity Criteria (NCI CTC) v4.0.

Could the sponsor provide a more detailed account of how one study centre reported a 46% rate of infusion-related reactions compared to rates of < 10% at other sites?

11.5.10.1. Sponsor's response

According to the sponsor's response, the Study CA209205 protocol did not provide a definition for *'infusion related reaction'.* However, the protocol was described as stating that such a reaction might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms and that infusion reactions were graded

according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.0) guidelines.

The sponsor provided a detailed description of the investigation of the high reporting rate of infusion reactions at Site 33 in the response to Question 18. The high rate was recognised at DBL in October 2015. Apparently, the sponsor held extensive discussion with clinical staff at Site 33 and the reason for this imbalance was investigated by the clinical team. The investigation ruled out errors in the infusion preparation practices, impact of infusion duration, potential batch product or filter quality issues, understanding of the adverse event reporting rules, and methodology followed to collect the information. One of the site sub-investigators speculated that the majority of events were likely to have been caused by the release of cytokines in Hodgkin involved areas during the treatment with nivolumab. According to this sub-investigator, the release of cytokines results in inflammatory-like symptoms and is often seen in patients treated at Site 33. According to the sub-investigator this was probably because the majority of patients treated at this site presented with a significant tumour burden (Stage III or IV disease) and the more tumour burden a patient has, the greater the likelihood that the patient will experience a reaction to any treatment.

This speculation was investigated by the sponsor who found that patients in Cohort B at Site 33 were overrepresented with Stage IV disease: 15/16 patients at Site 33 had Stage IV disease versus 54/80 patients in Cohort B overall.

11.5.10.2. Evaluator's response

The sponsor has provided some interesting speculation regarding possible cytokine release in patients with high tumour burden as the cause of infusion related reactions. However, the investigation does not explain why this was apparently seen at one site with Stage IV patients but was not apparently reported for the other 39 patients with Stage IV disease.

11.5.11. Question 36: Safety with subsequent allogeneic stem cell transplant

There were 5 patients in Study CA209039 who discontinued study drug to undergo allo-SCT. At the time of the interim analysis, 4 had died from complications of the allo-SCT. Two of these 4 patients had developed GVHD. In Cohort B of Study CA209205, 6 patients elected to stop the study drug and proceeded to SCT (allo-SCT: n = 5, ASCT: n = 1). Acute GVHD was reported in 3 subjects (Grade 1 or 2). All 6 subjects were alive at the time of the interim analysis. At the time of the interim analysis, there were no patients in Cohort A or C who had ceased nivolumab for subsequent SCT.

In the SCS, the sponsor has concluded that '*that nivolumab did not appear to have an adverse impact on safety in these patients*'. However, the FDA approved label for nivolumab includes the following in the 'Warnings and Precautions':

'Complications of allogeneic HSCT after Opdivo: Monitor for hyperacute graft-versus-host-disease (GVHD), grade 3-4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated adverse reactions. Transplant-related mortality has occurred. (5.10)'

The evaluator notes that Section 5.10 of the FDA-approved label refers to 17 patients who received allogeneic SCT following nivolumab and that the high level summary of the signal evaluation in the most recent PBRER refers to 34 patients who received allo-SCT after nivolumab therapy from Studies CA209039 and CA209205. The documents provided in this submission (interim CSRs and SCS) refer to 10 such patients. The sponsor is asked to provide an updated cumulative review of patients who have been received allo-SCT after prior nivolumab treatment, including any patients who have received intervening therapy(ies). This review should include a detailed analysis, conclusion, and justification of conclusion of an overall assessment of the risk. The evaluator notes that, depending on the information provided in response to this question, it may be appropriate to provide a similar warning in the 'Precautions' section of the Australian PI.

The evaluator also notes the FDA post market requirement to characterise the safety of allo-SCT in patients who have received prior nivolumab treatment for cHL.

Table 98. FDA post market requirement to characterise the safety of allo-SCT in patients who have received prior nivolumab treatment for cHL

Requirement/Commitment Number: 2

Required Under:	FDAAA Section 505(o)(3)
Original Projected Completion Date:	12/31/2022
Description:	Characterize complications after allogeneic hematopoietic stem cell transplantation (HSCT) following nivolumab in at least 90 patients with classical Hodgkin lymphoma, of which at least 50% had received nivolumab alone or in combination as the regimen immediately prior to the allogeneic HSCT conditioning regimen. Evaluate toxicities at least through transplant Day 180, and include details of prior nivolumab treatment and the transplant regimen. Characterize toxicities including hyperacute graft-versus-host disease (GVHD), severe (grade III-IV) acute GVHD, febrile syndromes treated with steroids, immune mediated adverse events, pulmonary complications, hepatic veno-occlusive disease, critical illness, and transplant-related mortality. Toxicities may be characterized prospectively, or through a combination of prospective and retrospective data analysis.
Current Status:	Pending

This report should be provided to the TGA when available.

11.5.11.1. Sponsor's response

The sponsor provided a review of patients who received allo-SCT following nivolumab treatment and confirmed that the results from the registry study in patients with allogeneic HSCT will be provided in a report when it is available.

The review noted that pre-clinical models showed the possibility that blockade of the PD-1/PD-L1 pathway may enhances GVHD, with a murine model indicating that inhibition of the PD-1/PD-L1 pathway enhanced GVHD lethality.

The number of patients who underwent subsequent allo-SCT is shown in Table 99, below.

Table 99. Number of subjects receiving allogenic HSCT

	Total From CA209205 and CA209039	CA209039	CA209205
Oct2015 DBL n=263	10	5	5
Apr2016 Direct Inquire to Sites upon FDA's request ⇒ USPI	17	5	12
June2016 DBL N=266	40*	5/23	35/243

*Database lock for CA209039 was 11-Aug-2015.

Among the 40 subjects who received a post-nivolumab allogeneic HSCT:

- 10 subjects received further salvage chemotherapy after nivolumab treatment and prior to allogeneic HSCT
- 30 subjects proceeded directly to allogeneic HSCT after nivolumab (without intervening chemotherapy)
- 7 patients had not had prior exposure to brentuximab vedotin (6 from Cohort A of Study CA209205 and one from Study CA209039)
- The source of cells was peripheral blood in 33 patients and bone marrow in 7
- The donor was a matched identical sibling in 6 patients
- The conditioning regimen was myeloablative in 4 patients and reduced intensity conditioning (RIC) in 27 and unknown in 9
- In vivo T-cell depletion was performed in 10 patients.

There were 6 deaths (15%, 6/40) reported after allogeneic HSCT. None of the reported deaths were due to disease progression; all the death events were therefore considered as transplant related mortality (TRM). Four of the deaths were reported in patients from Study CA209039 and 2 in patients from Cohort C of Study CA209205.

There were 18 patients (18/40, 45%) who experienced acute GVHD. The incidence and grade of acute GVHD in the 40 patients are shown in Table 100 below.

Table 100. Incidence and grade of acute GVHD in the 40 subjects who received allogeneic HSCT after nivolumab treatment (at any timepoint after allogeneic HSCT)

	Any grade	≥ Grade 2	≥ Grade 3
All subjects n=40	18 (45%)	13 (32.5%)	7* (17.5%)

Note: 2 subjects with acute GVHD were imputed to Grade 4.

Other complications of allo-SCT were described:

'Other complications following allogeneic HSCT

- *One subject was reported with hepatic veno-occlusive disease (VOD) who received reduced intensity conditioning and died due to multiorgan GVHD. The onset of the hepatic VOD was 11 days after allogeneic HSCT.*
- *Chronic GVHD was reported in 2 subjects; both are limited stage of chronic GVHD.*
- *Steroid-responive febrile syndrome, defined as fever (which may have been accompanied by skin, joint or liver symptoms) without infection, which responded to steroids was reported for 6 subjects.*
- *Two subjects experienced encephalitis: 1 case of Grade 3 lymphocytic encephalitis which occurred and resolved on corticosteroids, and 1 case of Grade 3 suspected viral encephalitis which resolved with antiviral therapy.'*

A comparison to historical data was provided.

Regarding TRM deaths: The cumulative incidence rate of TRM-related death (95% CI) at Day 100, and 1 year are 7.0 % (1.8, 25.3) and 33.4 % (11.9, 73.0), respectively for the 40 subjects who received allogeneic HSCT after discontinuation of nivolumab from CA209205 and CA209039. The sponsor referred to 5 population-based studies from the US, Europe, France, and Japan suggest 6% to 28% TRM at 100 days, and 20% to 46% TRM at 1-year in cHL patients post-allogeneic HSCT. According to the table provide by the sponsor, these studies included 40 to 285 patients. The highest 100day and 1 year mortality of 28% and 46% respectively was reported in a study of 73 patients who received myeloablative conditioning regimens. The other studies were of patients receiving RIC or a mixture of RIC and myeloablative conditioning (proportions not described).

Regarding acute GVHD: In the 40 subjects who received allogeneic HSCT after discontinuation of nivolumab in Studies CA209205 and CA209039, the cumulative incidence rate of Grade 2 to 4 aGVHD was 34.2 % (95% CI: 20.5, 53.4) at Day 100. The sponsor provided a table of the cumulative incidence rates reported in the same studies as those cited for TRM rates. These studies reported a cumulative incidence of any grade acute GVHD of 30 to 53% at 100 days. This was not broken down for Grade 2 to 4 acute GVHD.

The sponsor provided a discussion that noted that the initial assessment of the risk of allogeneic HSCT following nivolumab by the FDA was based on an updated assessment of 17 patients. An additional updated DBL of Study CA209205 in June 2016 provided additional patients (N = 40) and longer follow-up. According to the sponsor, the MAH assessed the data included in this response on 9 September 2016, and did not identify an increased risk of GVHD or transplant

related mortality. The sponsor also argued that there were other factors that may have contributed to the occurrence of GVHD in the nivolumab patients, for example 17/40 subjects had an unrelated donor and 12/40 had a two or more HLA mismatch related donor; peripheral blood, which has a much higher number of donor T lymphocytes compared to bone marrow, was the source of HSC for 33/40 of the patients and only 10/40 received T cell depletion following transplant.

The sponsor concluded that:

- In the most recent safety information, the rates of transplant related mortality and acute GVHD are consistent with the historical literature for this cHL patient population and that there were no new safety concerns identified with the increased numbers.
- Allogeneic HSC transplants are performed in specialized units by experts which mitigates the potential risk to patients. Transplant specialists are already well aware of the risk factors for GVHD and other complications and are expert in the management of the complications of allogeneic HSCT.
- The sponsor does not think that the proposed indication for nivolumab to treat cHL warrants a precaution in the Product Information regarding complications of allogeneic HSCT when it is used as subsequent therapy.

11.5.11.2. Evaluator's response

The evaluator is not convinced that there is no safety concern related to allo-SCT following nivolumab treatment in patients with cHL. There is a very wide range of TRM and aGVHD rates reported in the references cited by the sponsor. As noted by the sponsor, there are a number of factors that may contribute to aGVHD and TRM. The difficulty then lies in determining if like is being compared to like. However, if the small numbers reported in the cited studies were further divided into sub-groups to facilitate comparison of like to like, the numbers would be too small to be meaningful.

The evaluator has also been unable to confirm the sponsor's interpretation of the stance taken by the EMA, the sponsor has not provided any reports from the EMA; the EMA website (on 16 January 2017) does not include an EPAR for the cHL indication. However, the evaluator notes that:

- In the updated SmPC that became available on the EMA website on 12 January 2017, the section 'Special warnings and precautions' for use includes the following:

'Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT) in classical Hodgkin Lymphoma

Preliminary results from the follow-up of patients undergoing allogeneic HSCT after previous exposure to nivolumab showed a higher than expected number of cases of acute graft-versus-host-disease (aGVHD) and transplant related mortality (TRM). Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant related complications should be made case by case (see section 4.8).'

- The Nivolumab EU RMP version 5.6 includes complications of allogeneic haematopoietic stem cell transplant (HSCT) following nivolumab therapy (for cHL only) as an important potential risk

Given the signal in the preclinical models and the uncertainties in the comparison of the rates reported in the nivolumab clinical studies to historical data, the evaluator is of the opinion that a cautious approach should be taken with allogeneic stem cell transplant included as a 'Precaution' in the PI. This should have wording similar to that approved by the EMA. The evaluator considers that such a warning is appropriate for all clinicians who provide care for these patients, including transplant specialists, general oncologists and any clinicians who may be required to provide emergency care.

11.5.12. Question 37: Determining the impact of SAEs

A table [not included here] of the SCS Clinical Overview (second round correction by the evaluator) provides a comparison of SAEs across age groups for the pooled population treated with nivolumab monotherapy (n = 1991). According to this table, 8.7% of patients experienced fatal SAEs, 1.5% was life-threatening and 36.9% required hospitalisation/prolong hospitalisation. The evaluator requests that a similar presentation be provided for cHL patients (integrated SCE population and integrated cHL population using updated data) to enable comparison and to better assess the effects of SAEs.

11.5.12.1. Sponsor's response

The sponsor provided the response in a 23 page table that included all SAE categories for both cHL populations, with this broken down according to age group. There were 7 patients aged 65 years or more compared to 259 aged < 65 years. The sponsor notes that *'data from cHL patients 65 years of age or older are too limited to draw conclusions from the SCS (n = 266) and SCE (n = 95) populations with only 7 and 3 subjects, respectively, who were aged 65 years or older'.*

11.5.12.2. Evaluator's response

The intent of this question was to obtain data that helped describe the potential impact of nivolumab monotherapy in patients with cHL compared to patients with other tumour types, rather than to compare the impact across age groups within the cHL population.

From the table provided, and including data provided in the SCS, a comparison of the cHL populations to the pooled population treated with nivolumab monotherapy can be made for some of the categories of SAE (see Table 101 below).

Table 101. Comparison of SAE categories in cHL populations to all patients receiving nivolumab monotherapy

	SCE population (n = 95) %	All cHL patients (n = 266) %	All nivolumab monotherapy (n = 1991) %
SAE, all grade, all cause	30.5	25.6	41.7
SAE category			
Death	1.1	1.9	8.7
Life-threatening	0	0.8	1.5
Prolonged hospitalisation	28.4	24.1	36.9

Of the SAEs that required prolonged hospitalisation in 27 patients in the SCE population, 11 were due to infection (including pneumonia in 3 and meningitis in 2 patients), 3 were due to pyrexia and all other events were for single episodes. Of the SAEs that required prolonged hospitalisation in 64 patients from the SCS population, 21 were due to infection (including 6 with pneumonia, 2 with meningitis and 2 with parainfluenza infection), 4 were due to pleural effusion, 3 were due to pneumonitis, 4 were due to colitis/diarrhoea, 5 were due to infusion related reaction, 4 for pyrexia and in 2 patients each for dyspnoea, pancreatitis, hypercalcaemia, arrhythmia, pericardial effusion, febrile neutropaenia, rash.

11.6. PI/Indication

11.6.1. Question 38: Nivolumab versus brentuximab vedotin

The proposed wording of the second part of the indication proposes nivolumab as an alternative to brentuximab vedotin in patients who have had at least 2 prior therapies and who are not candidates for ASCT. The TGA approved indication for brentuximab vedotin is:

'Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

following autologous stem cell transplant (ASCT) or

following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option'.

The sponsor has not provided any substantive information to support the use of nivolumab in this setting and nivolumab has not been compared to brentuximab vedotin in this patient group. The evaluator recommends that the second part of the indication be removed.

If the sponsor is not in agreement with this, could evidence that supports the use of nivolumab in this setting and as an alternative to brentuximab vedotin be provided?

11.6.1.1. Sponsor's response

The sponsor confirms that no further data is available regarding the use of nivolumab in patients who have had at least two prior therapies and who are not candidates for ASCT. However, the sponsor accepts the TGA evaluator's recommendation on the second part of the indication (that is 'three prior therapies' instead of 'two prior therapies').

11.6.1.2. Evaluator's response

The sponsor's response is noted. See the evaluator's recommendations regarding a revised indication in Question 39 below.

11.6.2. Question 39: Wording of the indication in the PI

The evaluator is of the opinion that the wording of the PI should be changed such that:

1. Nivolumab is not proposed as an alternative to brentuximab vedotin in patients not suitable for ASCT, given that there is more evidence to support the use of brentuximab vedotin for this indication than there is for nivolumab.
2. A note to the indication that explicitly states the basis of the approval (surrogate end-point in small numbers of patients) is included.

The evaluator recommends that if nivolumab is approved for the proposed indication the indication wording should be:

'Opdivo as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL):

after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin, or

after at least three prior therapies, including brentuximab vedotin, in patients who are not candidates for ASCT

The approval for this indication is on the basis of objective response rate in 95 patients. Durability of response and any effect on progression free survival or overall survival have not been established'.

Is the sponsor in agreement with these proposed changes?

11.6.2.1. Sponsor's response

The sponsor agreed that the use of nivolumab should not be proposed as an alternative to brentuximab vedotin in patients not suitable for ASCT given that there is more evidence to support the use of brentuximab vedotin for this indication than there is for nivolumab.

The sponsor has agreed to the proposed changes with the exception of the wording and information included in the Note to Indication.

The sponsor has proposed:

> *'The approval for this indication is on the basis of objective response rate. Data on progression free survival and overall survival is limited'.*

On the basis that the number of patients in the dataset is not needed as '*this information is conveyed in the Clinical Trials section of the PI'* and that updated results confirm durability of the response.

The sponsor has also referred to Zykadia as a recent example of a Note to Indication statement recently approved by the TGA.

11.6.2.2. Evaluator's response

The evaluator notes that the sponsor has confirmed that there is no confirmatory Phase III study planned that will investigate the use of nivolumab monotherapy in patients with cHL, including the sub-group of patients who are ineligible for ASCT (see Question 2: Confirmatory Phase III study). The sponsor has also confirmed that there is no additional information to support the use of nivolumab monotherapy in patients who are ineligible for ASCT (see Question 38: Nivolumab versus brentuximab vedotin).

The 'Phase III registration trial' described by the sponsor is an open label Phase III study in patients with relapsed/refractory cHL that will investigate two treatment arms: brentuximab vedotin monotherapy versus brentuximab vedotin + nivolumab combination therapy. The study will not include a nivolumab monotherapy arm. The final analysis of Cohort A and Cohort C of Study CA209205 will provide some information regarding the efficacy of nivolumab as monotherapy in patients with relapsed/refractory cHL who have received ASCT.

Given that there will be no additional information forthcoming to support the use of nivolumab monotherapy in patients who are ineligible for ASCT the evaluator recommends that this part of the indication be removed. The evaluator notes that this is the approach that has been taken by both the FDA and the EMA.

With regard to the wording used in the Note to Indication, the evaluator accepts that the number of patients in the dataset is included in the 'Clinical Trials' section. The evaluator does not agree with the wording proposed by the sponsor in relation to PFS and OS but does acknowledge the example referred to by the sponsor where the wording of the Note to Indication was:

'Note to Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established'.[33]

The evaluator recommends that the wording of the indication be revised to:

> *'Opdivo as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.*
>
> *Note to cHL Indication: The approval for this indication is on the basis of objective response rate. An improvement in progression free survival or overall survival has not been demonstrated'.*

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

Substantial new clinical information has been presented. The sponsor's responses to clinical questions have provided updated efficacy and safety data over a longer period of follow-up with

[33] TGA approved PI for Zydakia.

database lock of February 2016 for Study CA209205 (median 15.44 months compared to median 8.9 months). However, it is concerning that the data from a subsequent DBL in June 2016 for Study CA209205 has not been used to provide the requested updated efficacy analysis. It is also concerning that the requested updated PFS and OS analysis for Study CA209039 was not provided (noting that the study protocol indicates that follow-up is to continue for 5 years).

Table 102. Second round assessment of benefits, strengths and uncertainties

Indication: ***'Opdivo, as monotherapy is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) following autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.'***	
Benefits	**Strengths and Uncertainties**
Improvement in ORR in Study CA209205 with: · ORR per IRRC = 53/80, 66.3% (95% CI 54.8, 76.4) ® No with CR = 6/80 ® No with PR = 48/80 With median follow-up of 15.4 months: · median duration of response (DOR) per IRRC 13.14 months (95% CI 8.74, NA) · median PFS 14.78 months (95% CI 11.33, NA) · median OS not reached	Strength: · Clinically important ORR with promising duration of response. Uncertainties: · Study design: Open label, non-comparator study with surrogate end-point and results based on outcomes of 80 patients · Low rate of CR (8.8%). Historically, treatments with high CR rates have had better patient outcomes · Translation to improved overall survival not known · Median OS not reached during median, 15.44 month follow-up · Median OS in patients with cHL relapsing after ASCT with current therapies estimated at approximately 2 years.
Improvement in ORR in Study CA209039 with: · ORR of 60% in comparable group ® No with CR= 0/15 ® No with PR = 9/15 · Estimated median duration of response 12 months (95% CI 1.8, NA)	Strength: · ORR result consistent across the two studies · Estimated median DOR clinically meaningful Uncertainties: · Open label, non-comparator study with surrogate end-point and results based on a group of 15 patients with cHL who have received prior ASCT followed by brentuximab vedotin who were recruited by chance · Retrospective analysis of tumour response by IRRC following late protocol amendment · No patient achieved CR.
Future studies to confirm the results of these early studies	There is no confirmatory study planned. A Phase III study of brentuximab vedotin + nivolumab versus brentuximab vedotin is planned. This will not include a nivolumab monotherapy arm and will not provide any further information regarding safety and efficacy for the proposed

Indication: ***'Opdivo, as monotherapy is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) following autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.'***	
Benefits	**Strengths and Uncertainties**
	indication. The efficacy results for Cohorts A and C from Study CA209205 have yet to be provided to the TGA. These will provide some additional information regarding efficacy in patients with relapsed/refractory cHL who have been treated with ASCT (Cohort A: patients who have received ASCT but not brentuximab vedotin; Cohort C: patients who have received ASCT and brentuximab vedotin but not in any specific order). The evaluator notes that in the response to question, the sponsor stated: '*A subsequent DBL for all 3 cohorts took place on 28 June 2016 after requisite minimum follow-ups for Cohorts A (9 months) was met*'. Safety data from this DBL has been provided, but no efficacy data
Indication: *'Opdivo, as monotherapy is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) [...] in patients who are not candidates for ASCT.'*	
Benefits	**Strengths and Uncertainties**
There were 5 patients in Study CA209039 who had not received prior ASCT. Of the 5 ASCT naïve patients, 4 had an objective response to nivolumab, with BOR per IRRC of CR (n = 3), PR (n = 1) and SD (n = 1).	Uncertainties: · The number of patients described in the dossier is too small to support the proposed indication · There will be no further information available regarding this indication from studies planned by the sponsor.

The main benefit offered by nivolumab in the treatment of patients with relapsed cHL after ASCT and brentuximab vedotin is a clinically important objective response rate of 66% with a median duration of response of 13 months. In the updated analysis for Cohort B of Study CA209205, after a median follow-up of 15 months, a median PFS of 14.8 months was reported and the median OS had not been reached. Given that the median overall survival of relapsed/refractory cHL with current therapies is estimated at 2 years, it is too early to say if nivolumab monotherapy will compare favourably with historical controls.

The evidence in support of nivolumab is limited to 80 patients from a Phase II study and 15 patients from a Phase I study. It is important to note that there is no confirmatory Phase III study planned. Future information to support this part of the indication will be limited to the ongoing PFS and OS assessments for both studies and to the efficacy results for Cohorts A and C from Study CA209205.

The evidence to support the second part of the indication is limited to 5 patients in the Phase I study. In the absence of any other supportive evidence and no future planned studies, the evaluator is of the opinion that the evidence is insufficient to support the use of nivolumab monotherapy in patients with relapsed cHL who are ineligible for ASCT.

The evaluator notes that nivolumab has received accelerated approval for the treatment of relapsed cHL after ASCT and brentuximab vedotin in the US and has more recently received full approval by the EMA. Both regulatory bodies revised the proposed indication and removed that part of the indication for patients who are ineligible for ASCT.

Table 103. Wording of the indication as approved by the FDA and EMA

FDA approved indication	*Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.*
EMA approved indication	*Opdivo is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.*

12.2. Second round assessment of risks

The sponsor's responses to clinical questions have provided updated safety data for Study CA209205 for a longer period of follow-up with database lock of June 2016 (median follow-up of 10 months for Cohort C, 14 months for Cohort A and 15 months for Cohort B).

After consideration of the responses to clinical questions, the risks of nivolumab in the proposed usage are largely unchanged from those identified in the first round assessment of risks (see Section 9.2, above). Table 104 (below) however, contains updated data and some new information from the sponsor's responses.

Table 104. Second round assessment of risks, strengths and uncertainties

Risks	Strengths and Uncertainties
Patients with cHL who have failed ASCT followed by brentuximab vedotin treated with nivolumab monotherapy (Cohort B of Study CA209205 and the ASCT-Bren Failed group in Study CA209039 n = 95): *Adverse Reactions:* · AEs, all cause, all grades reported in all patients (100%) · Grade 3 or 4 AEs, all cause, reported in 49.5% · SAEs, all cause, reported in 30.5%, with Grade 3 or 4 in 20% · Discontinuations due to AEs in 7 patients (7.4%) *Hospitalisation:* · Prolonged hospitalisation in 28% due to SAEs in the cHL SCE group (Cohort B of CA209205 + ASCT-Bren Failed group of CA209039)	Strengths: Despite the frequency of AEs, there was no apparent effect on average measures of QoL during the Weeks 9 to 33 of treatment Deaths recognised as resulting from nivolumab toxicity were rare; discontinuations due to AEs were infrequent. Uncertainties: · Reliability of results given small patient number and noting differences in reported AEs, Grade 3 or 4 AEs and SAEs between the two studies presented by the sponsor and between the two cHL populations (target cHL population and all cHL population) · Uncertainty regarding safety in the cHL SCE population in comparison to safety reported in other tumour types, noting the increased exposure in patients with cHL (due to reduced clearance and longer duration) · Generalisability of safety results to the wider

Risks	Strengths and Uncertainties
Death: · Deaths due to nivolumab toxicity reported in one patient (MSOF) (1.25%) although this was changed after database lock. *Narratives of deaths and SAEs suggest that irAEs were under-recognised and under-treated in some patients and may have contributed to deaths.* *Immune mediated AEs:* · All cause immune mediated AEs (up to 100 days post last dose and requiring treatment with immunosuppression) included: rash (14%), hypersensitivity (6.3%), pneumonitis (5.3%), hepatitis (5.3%), diarrhoea/colitis (1.1%), nephritis and renal dysfunction (0.4%) · All cause immune mediated endocrine AEs not requiring immunosuppression: hypothyroidism/thyroiditis (15.8%), adrenal insufficiency (1.1%) and hyperthyroidism (1.1%) *The immune mediated events of pneumonitis, toxic epidermal necrolysis, Stevens Johnson syndrome, hepatitis, encephalitis, myasthenia gravis, myositis, myocarditis and rhabdomyolysis have each been associated with fatal outcome in patients receiving nivolumab monotherapy.* *Increased risk of complications of allo-SCT:* · Potential increase in GVHD and other complications in patients having allo-SCT after nivolumab treatment.	population outside clinical studies, noting that: ® patients with ECOG >1 and patients with interstitial lung disease were excluded. ® immune mediated adverse reactions in some patients in the clinical trials had delayed recognition and management despite specific training and the investigator's brochure.

With the updated safety data, it is apparent, from discrepancies across the two cHL populations in the rates of Grade 3 to 4 AEs, SAEs and drug related AEs, that there are some uncertainties in the characterisation of the safety of nivolumab for the proposed indication. Discrepancies between the safety summaries of the two cHL populations and solid tumour populations also limit any generalisability from current experience with nivolumab. The possibility that safety may be worse in patients with cHL, both due to longer treatment duration and higher exposure per dose, cannot be excluded.

Determining the impact of nivolumab treatment on patients is difficult from the data provided. The narratives describe a number of patients with immune related AEs occurring both concurrently and sequentially. In some of these patients, adverse reactions that appear from the narratives to be immune related were not suspected by the investigator and treatment with immunosuppressive therapy was delayed. There were also some deaths that appeared to be due to immune related adverse reactions that had not been attributed to nivolumab treatment. The sponsor's response to one clinical question has indicated that around one third of cHL patients require prolonged hospitalisation during treatment with nivolumab. However, the rate of discontinuations due to AEs was low and the analysis of the quality of life measures found an average improvement to baseline for the first 33 weeks.

The proposed methods of distribution of the full PI remain a concern, given the dependence by the sponsor on third parties for availability of the electronic version. It is also concerning that while the sponsor's other documents, such as the Patient Alert Card and the irAR Management Guide, appropriately direct readers to consult the full PI, these documents do not provide internet addresses at which the electronic version can be found. A telephone number is provided but it is not clear to the evaluator as to whether this will be available on a 24 hours and 7 days a week basis.

The availability of the sponsor's irAR Management Guideline to clinicians is less of a concern now that other groups have developed management guidelines (for example, eviQ guidelines published in December 2016).

12.3. Second round assessment of benefit-risk balance

Patients with relapsed/refractory cHL following ASCT and brentuximab vedotin represent a group with unmet need and poor prognosis. Current treatment options may require a sequence of therapies to achieve a median overall survival of 2 years. In this setting, and despite the uncertainties regarding translation of the high ORR into improved overall survival, nivolumab treatment may provide an acceptable alternative treatment option.

The benefit-risk balance of nivolumab is favourable provided the changes recommended in the following 'Second round recommendation regarding authorisation' are adopted.

13. Second round recommendation regarding authorisation

The evaluator recommends that nivolumab be approved for the following indication:

> *'Opdivo as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.*
>
> *Note to cHL Indication: The approval for this indication is on the basis of objective response rate. An improvement in progression free survival or overall survival has not been demonstrated.'*

This favourable recommendation is contingent on:

- Changes to the indication as recommended by the evaluator being adopted.
- Changes to the product documentation as recommended by the evaluator being adopted.
- Updated PFS and OS analysis for Study CA209039 being provided to the TGA.
- Updated efficacy results for Cohort B and efficacy results for Cohorts A and C from Study CA209205 being provided to the TGA.

14. References

Alinari L, Blum KA. How I treat relapsed classical Hodgkin Lymphoma after autologous stem cell transplant. Blood 2016 127:287-295.

Australian Institute of Health and Welfare (AIHW) 2015. Australian Cancer Incidence and Mortality (ACIM) books: Hodgkin Lymphoma. Canberra: AIHW.

Australasian Bone Marrow Transplant Recipient Society Annual Data Summary 2014.

Australian Public Assessment Report for brentuximab vedotin; Proprietary Product Name: Adcetris. Sponsor: Takedo Pharmaceuticals Australia Pty Ltd. Date of AusPAR May 2014. Therapeutic Goods Administration.

Cheson, B et al. Revised Response Criteria for Malignant Lymphoma. 2007. J Clin Oncol;25(5):579-86.

CHMP Minutes for the meeting on June 20-23 2016. EMA; London, United Kingdom.

Committee for Medicinal Products for Human Use (CHMP) Assessment Report OPDIVO dated 23 April 2015.

Domingo-Domenech E, et al. Brentuximab Vedotin in Relapsed/Refractory Hodgkin's Lymphoma. European Oncology & Haematology, 2015;11(1):21–4

Eichenauer DA. Hodgkin's Lymphoma: ESMO Clinical Practice Guidelines. Ann Oncol (2014) 25 (suppl 3): iii70-iii75.

Fay A et al. (2016) The management of immune-related adverse events associated with immune checkpoint blockade, Expert Review of Quality of Life in Cancer Care, 1:1, 89-97.

Five-Year Survival Data Demonstrating Durable Responses from a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory Hodgkin Lymphoma (Abstract #2736, poster presentation on Sunday, December 6, 2015).

Gopal et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood. 2015;125(8):1236-1243.

Gravanis I et al. The European Medicines Agency Review of Brentuximab Vedotin (Adcetris) for the Treatment of Adult Patients with Relapsed or RefractoryCD30+ Hodgkin Lymphoma or Systemic Anaplastic Large Cell Lymphoma: Summary of the Scientific Assessment of the Committee for Medicinal Products for Human Use. The Oncologist 2016;21:102-109. Reference provided by the sponsor.

Guidance for Industry FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products.

Holmberg L et al. Brentuximab Vedotin Administered To Platinum-Refractory Transplant Naïve Hodgkin Lymphoma Patients Can Increase The Proportion Achieving FDG-PET Negative Status. Blood 2013 122:2106.

Li et al. Population pharmacokinetics of rituximab in patients with chronic lymphocytic leukaemia. J Clin Pharmacol 2012;52:1918-26.

Moskowitz et al. Brentuximab vedotin as consolidation therapy after autologous stem cell transplantation in patients with Hodgkin's Lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2015; 385: 1853-62.

NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma, Version 2.2016

Roemer M et al. PD-L1 and PD-L2 Genetic Alterations Define Classical Hodgkin Lymphoma and Predict Outcome. JCO JCO664482.

Sasse et al. Brentuximab vedotin (SGN-35) in patients with transplant-naive relapsed/refractory Hodgkin lymphoma. Leukaemia and Lymphoma Vol 54, Issue 10, 2013.

Shankar G, et al. Assessment and Reporting of the Clinical Immunogenicity of the Therapeutic Proteins and Peptides - Harmonized Terminology and Tactical Recommendations. The AAPS Journal 2014;DOI:10.1208/s12248-014-9599-2.

Sureda A et al. Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study - a prospective clinical trial by the Grupo Español de Linfomas/Trasplante de Médula Osea

(GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation," Haematologica, vol. 97, no. 2, pp. 310–317, 2012

Swann J, Smyth M. Immune surveillance of tumors. Journal of Clinical Investigation. 2007;117(5):1137-1146.

Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Translational Lung Cancer Research. 2015;4(5):560-575.

Viviani S et al. Brentuximab Vedotin (BV) an Effective Treatment for Autologous (ASCT) and/or Allogeneic (alloSCT) Transplant naïve Patients with Relapsed/Refractory (R/R) Hodgkin Lymphoma (HL): A retrospective Single-Institution Study; Blood Dec 2014, 124 (21) 5428.

Wolchok J, et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria Clin Cancer Res December 1, 2009 15:7412-7420.

Younes A, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol. 2012 Jun 20;30(18):2183-9.

Zinzani P. Brentuximab Vedotin in Transplant-Naïve Relapsed/Refractory Hodgkin Lymphoma: Experience in 30 Patients. Oncologist. 2015 Dec;20(12):1413-6.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au