



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for nivolumab

Proprietary Product Name: Opdivo

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

**October 2017**

**TGA** Health Safety  
Regulation

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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# Contents

<b>Common abbreviations</b>	<b>4</b>
<b>I. Introduction to product submission</b>	<b>8</b>
Submission details	8
Product background	8
Regulatory status	11
Product Information	13
<b>II. Quality findings</b>	<b>13</b>
<b>III. Nonclinical findings</b>	<b>13</b>
<b>IV. Clinical findings</b>	<b>13</b>
Introduction	13
Pharmacokinetics	15
Pharmacodynamics	17
Dosage selection for the pivotal studies	22
Efficacy	23
Safety	26
First Round Benefit-Risk Assessment	29
First Round Recommendation Regarding Authorisation	33
Clinical Questions	34
Second Round Benefit-Risk Assessment	34
<b>V. Pharmacovigilance findings</b>	<b>39</b>
Risk management plan	39
<b>VI. Overall conclusion and risk/benefit assessment</b>	<b>46</b>
Quality	46
Nonclinical	46
Clinical	46
Risk management plan	53
Risk-benefit analysis	53
Outcome	61
<b>Attachment 1. Product Information</b>	<b>62</b>
<b>Attachment 2. Extract from the Clinical Evaluation Report</b>	<b>62</b>

## Common abbreviations

Abbreviation	Meaning
ABMTRR	Australasian Bone Marrow Transplant Recipient Registry
ACPM	Advisory Committee on Prescription Medicines
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADRS	Adverse Drug-reaction Reporting System
AE	Adverse event
AER	Adverse Event Report
AIHW	Australian Institute of Health and Wellbeing
Allo-SCT	Allogeneic stem cell transplant
ALT	Alanine transaminase
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
ASCT	Autologous stem cell transplant
AST	Aspartate transaminase
$C_{avg,ss}$	Steady-state average concentration
cHL	Classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use (EU)
CI	Confidence interval
CL	Clearance
CLL	Chronic lymphocytic leukaemia
CR	Complete remission
CSR	Clinical Study Report
CT	Computed tomography

Abbreviation	Meaning
DBL	Database lock
DFCI	Dana Faber Cancer Institute
DHAP	Dexamethasone/High-dose Ara-C (cytarabine)/Platinum (cisplatin)
DOR	Duration of response
DRAE	Drug related adverse event
EBV	Epstein-Barr virus
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GVHD	Graft versus host disease
HCP	Healthcare Professional
HL	Hodgkin lymphoma
HSCT	Haematopoietic stem cell transplantation
ICE	Ifosfamide/Carboplatin/Etoposide
ICH	International Conference on Harmonisation
IGEV	Ifosfamide/Gemcitabine/Vinorelbine
IgG1	Immunoglobulin G1
IgG4	Immunoglobulin G4
IMAE	Immune mediated adverse event
IMAR	Immune mediated adverse reaction
IRAE	Immune related adverse event
irAR	Immune related adverse reaction
IRRC	Independent radiology review committee
IWG	International Working Group

Abbreviation	Meaning
K-M	Kaplan-Meier
LDH	Lactic dehydrogenase
MDS	Myelodysplastic syndromes
MMAE	Monomethyl auristatin E
MODS	Multiple organ dysfunction syndrome
MOF	Multiple organ failure
MSOF	Multiple system organ failure
NA	Not applicable
NBE	New Biological Entity
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin lymphoma
NSCLC	Non-small cell lung cancer
OESI	Other event of special interest
Opdivo	Nivolumab (tradenname)
ORR	Objective response rate
OS	Overall survival
PAC	Patient Alert Card
PBRER	Periodic Benefit-Risk Evaluation Report
PD-1	Programmed cell death-1 (receptor)
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PI	Product Information
PK	Pharmacokinetic(s)
PMR	Post-marketing requirement

Abbreviation	Meaning
PPK	Population pharmacokinetic(s)
PR	Partial remission
Pr(OR)	Probability of achieving an objective response
pSTAT3	Phosphorylated signal transducer and activator of transcription 3
PSUR	Periodic Safety Update Report
PT	Preferred Term
Q2W	Every 2 weeks
QoL	Quality of life
R-S	Reed-Sternberg (cell)
RCC	Renal cell carcinoma
RIC	Reduced intensity conditioning
RMP	Risk management plan
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Stable disease
SIRS	Systemic inflammatory response syndrome
SJS	Stevens-Johnson syndrome
SRR	Safety Related Review
TEN	Toxic epidermal necrolysis
TNF	Tumour necrosis factor
US	United States
VOD	Veno-occlusive disease
Yervoy	Ipilimumab (tradenname)

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	26 May 2017
<i>Date of entry onto ARTG</i>	30 May 2017
<i>Active ingredient:</i>	Nivolumab
<i>Product name:</i>	Opdivo
<i>Sponsor's name and address:</i>	Bristol-Myers Squibb Australia Pty Ltd Level 2, 4 Nexus Court Mulgrave VIC 3170
<i>Dose form:</i>	Concentrate solution for injection
<i>Strength:</i>	40 mg in 4 mL (10 mg/mL); and 100 mg in 10 mL (10 mg/mL)
<i>Container:</i>	Glass vial
<i>Pack size:</i>	1 vial per pack
<i>Approved therapeutic use:</i>	<i>Opdivo, as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant and treatment with brentuximab vedotin. The approval of this indication is based on objective response rate. See Clinical Trials.</i>
<i>Route of administration:</i>	Intravenous infusion
<i>Dosage:</i>	Recommended dose of Opdivo as monotherapy is 3 mg/kg administered intravenously (IV) over 60 minutes every 2 weeks (Q2W). Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.'
<i>ARTG number (s):</i>	231867, 231868

## Product background

This AusPAR describes the application by the sponsor to register Opdivo nivolumab concentrate solution for IV infusion indicated for:

*'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.'*



The indications for Opdivo nivolumab currently approved in Australia (since January 2016) are:

*'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.*

*As monotherapy for the treatment of patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy in adults.'*

The proposed dosage of Opdivo as a monotherapy is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody which binds to the programmed cell death protein-1 (PD-1), a cell surface receptor and blocks its interaction with programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2). The PD-1 receptor is a negative regulator of T cell activity. Nivolumab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to the PD-L1 and PD-L2 ligands.

### **Classical Hodgkin lymphoma**

Hodgkin lymphoma (HL) is an uncommon B cell lymphoid malignancy. 'Classic' Hodgkin lymphoma (cHL) is the more common entity, a monoclonal lymphoid malignancy characterised by the presence of multinucleated Reed-Sternberg (R-S) cells, mostly of B cell origin and accounting for 1 to 10% of the cells in the tumour tissue. PD-1 ligands PD-L1 and PD-L2 are overexpressed by R-S cells in cHL.

The remaining cells are a mixed infiltrate of various lymphoid cells, including regulatory T cells and macrophages. 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 (TNF) receptor superfamily.

The 2011 incidence/2012 mortality rates for HL in Australia were 606 and 78, respectively. The age adjusted incidence rate for this period is 2.7/100,000 population.<sup>1</sup>

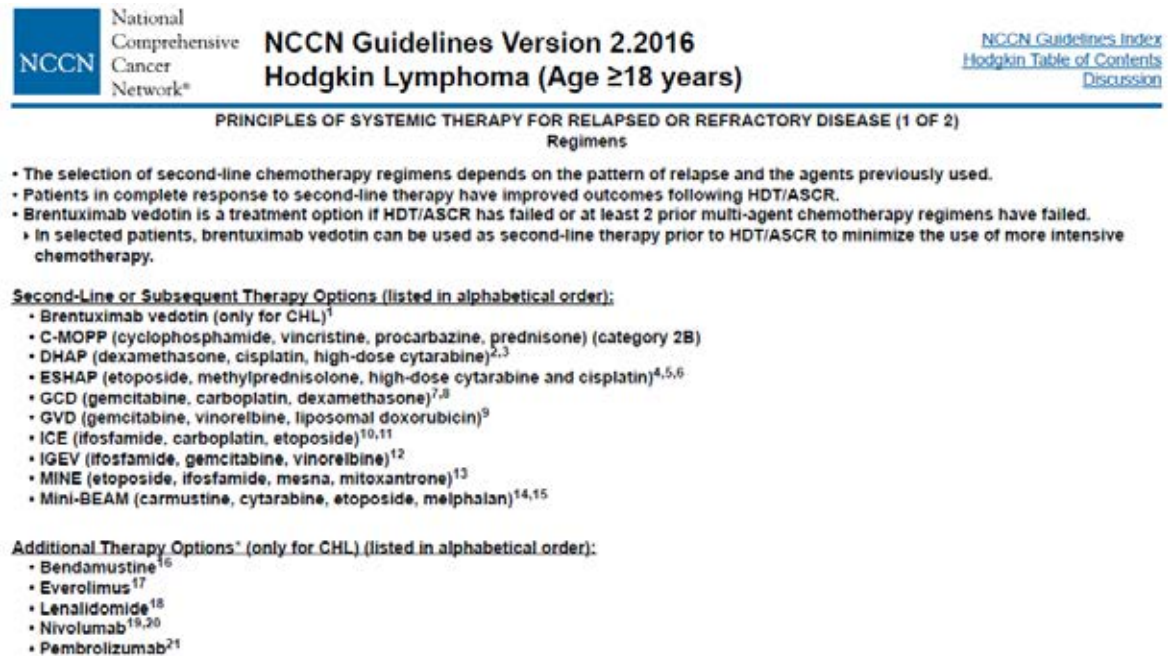
### **Current treatments**

Patients presenting with advanced stage disease may receive combined chemotherapy and radiotherapy. Patients who do not respond to front line therapy or who relapse following an initial response to frontline therapy (relapsed or refractory HL) are generally treated with high dose 'salvage' chemotherapy followed by autologous stem cell transplantation (ASCT). Salvage chemotherapy regimens including as DHAP (dexamethasone/high-dose

<sup>1</sup> Australian Institute of Health and Wellbeing (AIHW) Cancer in Australia, An Overview 2014. Canberra, Australia: AIHW; 18 December 2014.

Ara-C/cisplatin), IGEV (ifosfamide/gemcitabine/vinorelbine), or ICE (ifosfamide/carboplatin/etoposide) are given to reduce the tumour burden and determine eligibility for ASCT (as shown in Figure 1 below).<sup>2</sup> The sponsor's Clinical Overview described ASCT as the standard of care 'which can induce long-term remission in approximately 50% of patients'.

**Figure 1. Excerpt from the NCCN Guideline for Hodgkin Lymphoma**



NCCN National Comprehensive Cancer Network®

**NCCN Guidelines Version 2.016**  
**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)<sup>1</sup>
- C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) (category 2B)
- DHAP (dexamethasone, cisplatin, high-dose cytarabine)<sup>2,3</sup>
- ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin)<sup>4,5,6</sup>
- GCD (gemcitabine, carboplatin, dexamethasone)<sup>7,8</sup>
- GVD (gemcitabine, vinorelbine, liposomal doxorubicin)<sup>9</sup>
- ICE (ifosfamide, carboplatin, etoposide)<sup>10,11</sup>
- IGEV (ifosfamide, gemcitabine, vinorelbine)<sup>12</sup>
- MINE (etoposide, ifosfamide, mesna, mitoxantrone)<sup>13</sup>
- Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)<sup>14,15</sup>

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

- Bendamustine<sup>16</sup>
- Everolimus<sup>17</sup>
- Lenalidomide<sup>18</sup>
- Nivolumab<sup>19,20</sup>
- Pembrolizumab<sup>21</sup>

In Australia in 2015, there appeared to be fewer than 70 haematopoietic cell transplants for HL in recipients aged  $\geq 16$  years.<sup>3</sup>

For patients failing high dose chemotherapy and ASCT, brentuximab vedotin (Adcetris) is an option registered in Australia. The sponsor's Clinical Overview stated: *'The median overall survival (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 pre-treated 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'*.

Brentuximab vedotin is an antibody drug conjugate (ADC) consisting of three components: an immunoglobulin G1 (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.

In December 2013, brentuximab vedotin was approved in Australia for the indications of:

*'Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):*

*following autologous stem cell transplant (ASCT) or*

<sup>2</sup> NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma (Version 2.016): NCCN; 29 April 2016. The National Comprehensive Cancer Network (NCCN) is a non-profit alliance of 27 cancer centres in the United States, most of which are designated by the National Cancer Institute (one of the United States National Institutes of Health) as comprehensive cancer centres.

<sup>3</sup> Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) Australasian Bone Marrow Transplant Recipient Registry: Annual Data Summary 2015. Darlinghurst, NSW Australia: ABMTTR; 2016.

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).<sup>4</sup>

The sponsor provided an updated summary of the use of agents reported in prospective studies over 15 years (shown in Table 1, below) to include bendamustine, GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin) and lenalidomide in addition the other 6 agents in the original sponsor provided summary.

**Table 1. Sponsor's updated summary of treatments of relapsed or refractory HL after ASCT from prospective studies within the past 15 years**

Agent(s)	Pub Date	Target Population	No. Treated	Prior ASCT	ORR (%)	CR (%)	PFS	DOR	Overall Survival
Bendamustine <sup>7 e</sup>	2013	Relapsed Refractory HL (median lines of prior therapy=4)	34	27	56%	35%	5.2 months (median)	5 months (median)	NS
Brentuximab vedotin <sup>8</sup>	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 <sup>9</sup>	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 <sup>10</sup>	2011	Relapsed Refractory HL	36	31	19%	3%	4 months (median)	6 months	20 months (median)
Everolimus <sup>11</sup>	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 <sup>12</sup>	2007	Relapsed Refractory HL	91	36	75%	17%	EFS: 8.5 months 4 Year PFS: ~10% (36 subjects)	NS	4 Year OS: 34%
Bortezomib <sup>13</sup>	2006	Relapsed Refractory HL with 2 prior regimens including stem cell transplant	14	13	7%	0	NS	NS	NS
Gemcitabine <sup>14</sup>	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 <sup>15</sup>	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.

## Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 11 January 2016. Nivolumab has been registered for several malignancy indications (as listed in the product background, above) all with evidence from Phase III trials. Nivolumab does not have orphan designation.

The approved Australian PI provides the currently accepted pharmacology, efficacy and safety information relevant to these registered indications, available as Attachment 1 to this document.

The most recent consideration of Opdivo nivolumab by the TGA's Advisory Committee on Prescription Medicines (ACPM) was at Meeting 312 in October 2016.<sup>5</sup> The resolution passed recommended approval for the indication for treatment of adult patients with

<sup>4</sup> Australian Public Assessment Report (AusPAR) for Adcetris brentuximab vedotin Takeda Pharmaceuticals Australia Pty Ltd. TGA: Canberra, Australia; 19 May 2014.

<sup>5</sup> The Advisory Committee on Medicines (ACM) was established in January 2017, to encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM).

advanced clear cell renal cell carcinoma (RCC) who had received prior antiangiogenic therapy.

At the time the TGA considered this application similar applications had been approved in the United States (US) and the European Union (EU) and are discussed below.

As of 17 May 2016, the US Food and Drug Administration (FDA) has approved the use of nivolumab (3 mg/kg every two weeks until progression or unacceptable toxicity):

*'for the treatment of patients with classical Hodgkin lymphoma that has relapsed or progressed after autologous haematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin'.<sup>6</sup>*

The labelled indication describes it as having been 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 clinical trials.'*

The FDA approval letter includes the accelerated approval requirement for further adequate and well-controlled studies/clinical trials; specifically the post-marketing requirement (PMR) 3089-1 to conduct a Phase III clinical trial verify and isolate the clinical benefit of nivolumab in patients with cHL, with expected protocol submission in February 2017 and primary progression-free survival (PFS) analysis in September 2024.<sup>7</sup>

The letter also notes *'higher than expected occurrences of serious complications in patients who receive allogeneic hematopoietic stem cell transplantation after Opdivo (nivolumab)',* resulting in PMR 3089-2 to characterise *'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 to 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.'*

The sponsor was to have provided a final protocol submission to FDA by December 2016. It appears to the Delegate that this requirement relates to registry Study CA209835 described in the pharmacovigilance plan.

The most recent FDA approved label includes details of observed adverse events (AE) including immune mediated adverse reactions (IMAR) in clinical trials for each specific indication.<sup>8</sup>

In the EU, the cHL indication was approved by the European Medicines Agency (EMA) as follows:

*'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'.<sup>9,10</sup>*

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<sup>6</sup> United States Food and Drug Administration (US FDA). Labelling and Prescribing Information for Opdivo (nivolumab), Reference ID: 3932569. US FDA; May 2016.

<sup>7</sup> Department of Health and Human Services. Prior Approval and Accelerated Approval Requirements Letter, Supplemental Biologics License Application (sBLA) 125554, supplement 019. US FDA; 17 May 2016.

<sup>8</sup> United States Food and Drug Administration (US FDA). Labelling and Prescribing Information for Opdivo (nivolumab), reference ID: 4050515. US FDA; February 2017.

## Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Quality findings

No new quality data were provided or evaluated with this submission.

## III. Nonclinical findings

No new nonclinical data were provided or evaluated with this submission.

## IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

## Introduction

### Clinical rationale

The sponsor's Clinical Overview provides a Product Development Rationale. This includes a brief overview of HL 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 pre-treated 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'*.

A 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 1, above).

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.

### 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.

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<sup>9</sup>. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Opdivo, nivolumab (EMA/CHMP/741329/2016). European Medicines Agency (EMA) London, United Kingdom; 13 October 2016.

<sup>10</sup> Committee for Medicinal Products for Human Use (CHMP). Summary of Product Characteristics (SmPC), Annex I for Opdivo, nivolumab. European Medicines Agency (EMA) London, United Kingdom.

According to 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.

### **Contents of the clinical dossier**

The clinical dossier contained the following:

- Interim Clinical Study Report (CSR) for Study CA209205
- Interim CSR 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 (RCC, melanoma, and NSCLC)
- Population Pharmacokinetic (PPK) 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 (SCE) (both dated February 2016); and a Clinical Overview of cHL.

### **Paediatric data**

This submission included no paediatric data.

### **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'*.<sup>11,12</sup>

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<sup>11</sup> Directive 2001/20/EC of the European Parliament and Council (4 April 2001) on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

<sup>12</sup> ICH = International Conference on Harmonization (of Technical Requirements for Pharmaceuticals for Human Use); GCP = Good Clinical Practice, an international quality standard provided by the ICH.

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## Pharmacokinetics

### 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 '*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 exposure-response 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 efficacy analysis and one exposure-response safety analysis.

### Evaluator's 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 Eastern Cooperative Oncology Group (ECOG) Performance Status > 1 have been excluded from the clinical studies.<sup>13</sup>

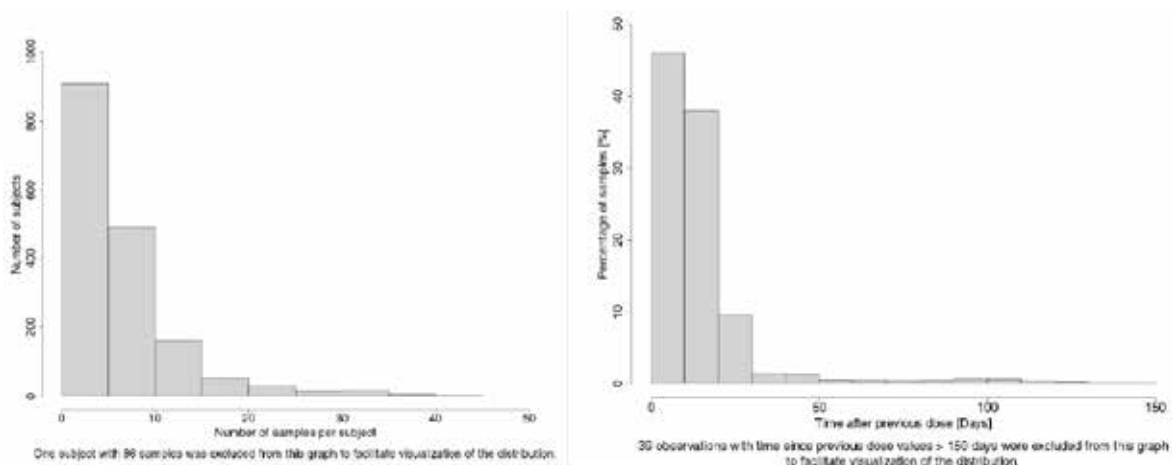
Pharmacokinetic studies in the clinical development programme have largely consisted of sparse sampling of serum nivolumab concentrations, with these results used in a sequence of PPK analyses. Use of the sparse sampling model and dependence on PPK modelling is demonstrated in the following figures from 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).

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<sup>13</sup> Oken M et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. December 1982; 5(6):649-55.

The Eastern Cooperative Oncology Group (ECOG) score (published in 1982 is a 6 grade scale, with 0 denoting perfect health and 5 death. A score of 1 is equivalent to symptomatic but completely ambulatory (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work).

**Figure 2. Distribution of number of samples per patients and the number of samples according to time since dose**



According to the sponsor's documents, the PPK 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 (shown in Table 2, below) 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 PPK 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 steady state average concentration ( $C_{avg,ss}$ )).

**Table 2. 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
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 describes higher clearance of rituximab in patients with non-Hodgkin lymphoma (NHL) compared to patients with CLL and suggests that a higher dose of rituximab may be required in patients with chronic lymphocytic leukaemia (CLL).<sup>14</sup> The increase in nivolumab exposure in patients with cHL was assessed by the sponsor as not being clinically meaningful, *'as the exposure-response safety analysis demonstrated that exposure was not a predictor of the risk of Grade 3+ DRAEs, 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 clinical 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 Product Information (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 (see Clinical Questions in Attachment 2 for further details).

## Pharmacodynamics

### Studies providing pharmacodynamic data

Both Study CA209039 and Study CA209205 provided limited new pharmacodynamic data. These studies are described under 'Clinical efficacy' of Attachment 2.

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

### Evaluator's conclusions on pharmacodynamics

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

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<sup>14</sup> Li et al. Population pharmacokinetics of rituximab in patients with chronic lymphocytic leukaemia. J Clin Pharmacol 2012; 52:1918-26.

- 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.

***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 'Dana Faber Cancer Institute (DFCI) assay', phosphorylated signal transducer and activator of transcription 3 (pSTAT3) status by 'DFCI assay' and Epstein-Barr virus (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 PD-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 3. 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%)
Patients with PD-L1 expression $\geq$ 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 (objective response rate (ORR) by the independent radiology review committee (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% confidence interval (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.

#### ***Time course of tumour response***

In both studies of patients with cHL, all patients who responded to nivolumab showed this response (using the International Working Group (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 'best overall response' (BOR) per investigator, 3 of these subjects were subsequently classified as responders (partial remission (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 allogeneic stem cell transplant (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.

#### ***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  $C_{avg,ss}$ , with this calculated from the PK simulation. Of note is that the analyses include different populations of subjects: the PPK study and the exposure-response safety analysis both include all 23 subjects from Study CA209039 and 170 subjects from Study CA209205 (from Cohorts A, B and C); the exposure-response 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, baseline weight, ECOG status, and number of prior therapies did not appear to affect the probability of achieving an objective response (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 fifth 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 ninety-fifth 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 exposure-response curve*' regardless of the assessment modalities.

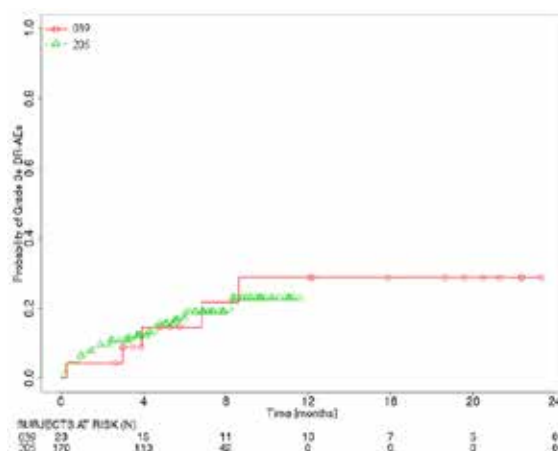
The report expressed concern that the relationship between efficacy and exposure may be unreliable '*due to the limited range of exposures in the analysis data, as all subjects were assigned the same nivolumab dosing regimen of 3 mg/kg Q2W and the sensitivity analysis indicated that only a few subjects were influential in explaining the discrepancy between the exposure-response 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+ drug related adverse events (DRAE) in patients with cHL.
- The covariate ECOG status was found to be a significant predictor of experiencing a Grade 3+ DRAE as a subject with ECOG score of 1 was twice as likely to experience a Grade 3+ DRAE 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+ DRAEs, as indicated by the hazard ratio coefficient of 0.7949 (95% CI 0.2219, 2.847).

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

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



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.

### ***Analysis of immunogenicity***

Only one patient in each of Studies CA209205 and CA209039 tested anti-drug antibody (ADA) positive state during treatment with nivolumab. However, there were 7/159 (4.4%) of patients in Study CA209205 and 3/19 (15.8%) of patients in Study 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 sponsor's Summary of Clinical Pharmacology provides a summary of select AEs 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 4, below).

**Table 4. 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.

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.<sup>15</sup> Of concern to the clinical 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

<sup>15</sup> 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.



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 CA209039 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 ADAs. The evaluator is of the opinion that this capacity for nivolumab to trigger an IMAR needs further exploration and discussion.

### ***Pharmacodynamic interactions***

No investigations of pharmacodynamic 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 autoimmune diseases were excluded from the studies. Patients who developed immune related adverse reactions (irAR) during, or following treatment, could be treated with immune suppressive therapy/therapies. A separate efficacy analysis for these patients has been requested.

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 subgroup 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.

### **Dosage selection for the pivotal studies**

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.

The sponsor's 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 60 minutes 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 maximum tolerated dose 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.'*

The Study CA209003 CSR was provided to the TGA with the first nivolumab New Biological Entity (NBE) submission. In this dose-ranging study, patients with solid organ tumours (melanoma, RCC, 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 version 1.0 criteria, and consisted primarily of the objective response rate (ORR).<sup>16</sup> 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 every two weeks 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.

## Efficacy

### Studies providing efficacy data

The interim CSRs for Studies CA209205 and CA209039 along with an integrated analysis provided efficacy data.

### Evaluator's conclusions on efficacy

As the proposed indication is in two parts, the following summary of efficacy is also presented in two parts. Please see Attachment 2 for further details of the clinical evaluator's conclusions on efficacy.

#### ***First part of 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.'*

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.

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<sup>16</sup> Therasse P et al. New guidelines to evaluate the response to treatment in solid tumors (RECIST Guidelines). J Natl Cancer Inst 2000;92:205-16.

The primary efficacy endpoint of each analysis was the surrogate endpoint of objective response rate (ORR) 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 (OS) and progression free survival (PFS) were exploratory or secondary end-points in each study. No comparator was provided in either study.

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 months.

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 historical 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.

Allo-SCT 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 OS 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 AusPAR for brentuximab vedotin.<sup>4</sup> 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 OS was 41% and the estimated median OS 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.

### **Second part of indication**

*'the 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 criterion for Cohort B in Study CA209205. However, in Study CA209039, the main inclusion criterion 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 New Chemical Entity 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).<sup>17</sup>

As described in the Background section of the CER (see Attachment 2), 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 ORR 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.

## Safety

### Studies providing 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 (PSUR) and Periodic Benefit-Risk Evaluation Report (PBRER) 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 (SRR) 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 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 (AER) in the TGA's Adverse Drug-reaction Reporting System (ADRS) for nivolumab.

### Patient exposure

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

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<sup>17</sup> Australian Public Assessment Report (AusPAR) for brentuximab vedotin. Therapeutic Goods Administration (TGA) Canberra, Australia; May 2014.

(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). Patient exposure is shown in Tables 8 and 9 below.

**Table 8. Exposure to nivolumab in Studies CA209039 and CA209205**

	Study CA209039			Study CA209205			
	cHL ASCT Bren-failed <sup>1</sup> N = 15	cHL other N = 8	cHL all N = 23	Cohort A N = 63	Cohort B <sup>1</sup> 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
Number 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 9. 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)

The SCS provides the following comparison across tumour types, shown in Table 10 below. Note that the integrated cHL population (including patients from Cohort A and C of Study CA209205) is used in this comparison.

**Table 10. Cumulative dose and exposure to nivolumab across tumour types**

	cHL N = 263	ROC N = 406	Melanoma N = 787	NSCLC N = 535
<b>NUMBER OF DOSES RECEIVED</b>				
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 - 49)	6.0 (1 - 52)
<b>CUMULATIVE DOSE (MG/RS)</b>				
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)
<b>RELATIVE DOSE INTENSITY</b>				
>= 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)
<b>DURATION OF THERAPY (MONTHS)</b>				
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 ( 82.5)	455/787 ( 57.8)	456/535 ( 85.2)
<b>OTHER STATISTICS</b>				
MEAN	5.367	8.847	6.967	5.405
STANDARD DEVIATION	4.1322	7.7998	5.2302	6.0416
> 3 MONTHS (%)	181 ( 68.8)	294 ( 72.4)	519 ( 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)
<b>TOTAL EXPOSURE (P-Y)</b>	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); ROC: 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.

### Safety issues with the potential for major regulatory impact

A detailed analysis of the safety issues with the potential for major regulatory impact is available in Attachment 2.

### Post-marketing data

A detailed analysis of safety issues related to post-marketing data is available in Attachment 2.

### **Evaluator's conclusions on safety**

The following provides a summary of the clinical evaluator's conclusions on safety. Please see Attachment 2 for further details.

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  $\geq 90\%$  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  $\pm$  immunosuppressive therapy. However, there are patients who have more severe manifestations of these events, requiring hospitalisation and having a 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 DBL 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.

### **First Round Benefit-Risk Assessment**

The following tables provide a summary of the benefits, and risks as assessed by the clinical evaluator at the first round. Please see Attachment 2 for further details.

#### **First round assessment of benefits**

A summary of the clinical evaluator's first round assessment of benefits, along with the strengths and uncertainties of the evidence for those benefits for the first and second parts of the proposed indication are shown in Tables 11 and 12 respectively.

**Table 11. First round assessment of benefits (first part of indication)**

<b>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</b>	
<b>Benefits</b>	<b>Strengths and Uncertainties</b>
<p>Improvement in ORR in Study CA209205 with:</p> <ul style="list-style-type: none"> <li>• ORR per IRRC = 53/80, 66.3% (95% CI 54.8, 76.4)               <ul style="list-style-type: none"> <li>– Number with CR = 7/80</li> <li>– Number with PR = 46/80.</li> </ul> </li> <li>• Estimated median duration of response (DOR) 7.8 months (95% CI 6.64, NA).</li> </ul> <p>Note: 31/53 responders per IRRC were still on treatment and censored prior to the analysis.</p>	<p>Strength: Clinically meaningful ORR.</p> <p>Uncertainties:</p> <ul style="list-style-type: none"> <li>• Study design: Open label, non-comparator study with surrogate end-point and results based on outcomes of 80 patients.</li> <li>• Study conduct: Questions regarding study conduct at two sites responsible for treating 21/80 patients.</li> <li>• Low rate of CR (8.8%). Historically, treatments with high CR rates have had better patient outcomes.</li> <li>• 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.</li> <li>• Translation to improved overall survival not known; median OS not reached during a median of 9 months follow-up. Median OS in patients with cHL relapsing after ASCT with current therapies estimated at approximately 2 years.</li> <li>• Clinical importance of the results; historically ORRs of 50 to 70 have been reported for a number of treatment options in relapsed or refractory cHL, together with median DORs of 5 to 7 months.</li> </ul>
<p>Improvement in ORR in Study CA209039 with:</p> <ul style="list-style-type: none"> <li>• ORR of 60% in comparable group               <ul style="list-style-type: none"> <li>– No with CR= 0/15</li> <li>– No with PR = 9/15.</li> </ul> </li> <li>• Estimated median duration of response 12 months (95% CI 1.8, NA).</li> </ul>	<p>Strengths:</p> <ul style="list-style-type: none"> <li>• ORR result consistent across the two studies.</li> <li>• Estimated median DOR clinically meaningful.</li> </ul> <p>Uncertainties:</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Retrospective analysis of tumour response by IRRC following late protocol amendment.</li> <li>• No patient achieved CR.</li> </ul>
<p>Future studies to confirm the results of these early studies.</p>	<p>Uncertainty: Confirmatory study. The sponsor has provided written advice to the TGA that no confirmatory studies are planned: [The sponsor] <i>'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'</i>.</p>

**Table 12. First round assessment of benefits (second part of indication)**

<b>Indication:</b> <i>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.</i>	
<b>Benefits</b>	<b>Strengths and Uncertainties</b>
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).	<p>Uncertainties:</p> <ul style="list-style-type: none"> <li>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.</li> <li>Current phrasing of this part of the indication would allow nivolumab to be used instead of the more established brentuximab vedotin.</li> </ul>

**First round assessment of risks**

Table 13 summarises the clinical evaluators first round assessment of risks along with the strengths and uncertainties based on the available evidence.

**Table 13. First round assessment of risks**

<b>Risks</b>	<b>Strengths and Uncertainties</b>
<p>Patients with cHL who have failed ASCT followed by brentuximab vedotin treated with nivolumab monotherapy for Cohort B of Study CA209205:</p> <ul style="list-style-type: none"> <li>Adverse reactions, all cause, all grades reported in almost all patients (&gt; 98%). Most common reactions: fatigue 36%, pyrexia 31%, cough 27.5%, diarrhoea 27.5%, nausea 24%.</li> <li>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%).</li> <li>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.</li> <li>Discontinuations due to AEs in 3 patients (3.8%).</li> <li>Deaths due to nivolumab toxicity reported in</li> </ul>	<p>Strengths:</p> <ul style="list-style-type: none"> <li>Despite the frequency of AEs, there was no apparent effect on average measures of QoL during Weeks 9 to 33 of treatment.</li> <li>Deaths and discontinuations due to nivolumab toxicity were rare.</li> </ul> <p>Uncertainties:</p> <ul style="list-style-type: none"> <li>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.</li> <li>Generalisability to target population, noting that patients with ECOG &gt; 1 and patients with interstitial lung disease were excluded.</li> <li>Generalisability from safety as established in patients with solid tumours to patients with cHL, noting increased duration of</li> </ul>



Risks	Strengths and Uncertainties
<p>one patient (MSOF) (1.25%) although this was changed after DBL.</p> <p>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.</p> <p>There was one other death attributed to nivolumab toxicity, MSOF following <i>Pneumocystis jiroveci</i> pneumonia.</p> <p>Possible increase in GVHD and other complications in patients having allo-SCT after nivolumab treatment.</p> <p>The immune mediated events of pneumonitis, TEN, SJS, hepatitis, encephalitis, myasthenia gravis, myositis, myocarditis and rhabdomyolysis have each been associated with fatal outcome in patients receiving nivolumab monotherapy.</p>	<p>treatment and different PK in patients with cHL.</p> <ul style="list-style-type: none"> <li>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.</li> </ul>

### First round assessment of benefit-risk balance

#### **Benefits**

The main benefit offered by nivolumab in the treatment of patients with relapsed cHL (after ASCT and brentuximab vedotin) is an ORR 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.

#### **Risks**

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.



## First Round Recommendation Regarding Authorisation

This clinical evaluator is unable to make a recommendation at this time.

### Issues

#### *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.

#### **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  $C_{avg,ss}$ ). 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  $\pm$  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, the sponsor's responses to these questions will further assist in the assessment of safety.

## Clinical Questions

For details of the clinical evaluator's questions, sponsor's responses, and the evaluation of these responses please see Attachment 2.

## Second Round Benefit-Risk Assessment

### Second round assessment of benefits

Substantial new clinical information has been presented. The sponsor's responses to clinical questions (see Attachment 2) have provided updated efficacy and safety data over a longer period of follow-up with DBL 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).

A summary of the clinical evaluator's second round assessment of benefits, along with the strengths and uncertainties of the evidence for those benefits for the first and second parts of the proposed indication are shown in Tables 14 and 15 respectively.

**Table 14. Second round assessment of benefits**

<b>Indication:</b> <i>'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.'</i>	
<b>Benefits</b>	<b>Strengths and Uncertainties</b>
<p>Improvement in ORR in Study CA209205 with:</p> <ul style="list-style-type: none"> <li>• ORR per IRRC = 53/80, 66.3% (95% CI 54.8, 76.4)               <ul style="list-style-type: none"> <li>– No with CR = 6/80</li> <li>– No with PR = 48/80</li> </ul> </li> </ul> <p>With median follow-up of 15.4 months:</p> <ul style="list-style-type: none"> <li>• median duration of response (DOR) per IRRC 13.14 months (95% CI 8.74, NA)</li> <li>• median PFS 14.78 months (95% CI 11.33, NA)</li> </ul>	<p>Strength:</p> <ul style="list-style-type: none"> <li>• Clinically important ORR with promising duration of response.</li> </ul> <p>Uncertainties:</p> <ul style="list-style-type: none"> <li>• Study design: Open label, non-comparator study with surrogate end-point and results based on outcomes of 80 patients</li> <li>• Low rate of CR (8.8%). Historically, treatments with high CR rates have had better patient outcomes</li> <li>• Translation to improved overall survival not known</li> </ul>

<b>Indication:</b> <i>'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.'</i>	
<ul style="list-style-type: none"> <li>• median OS not reached.</li> </ul>	<ul style="list-style-type: none"> <li>• Median OS not reached during median 15.44 months follow-up. Median OS in patients with cHL relapsing after ASCT with current therapies estimated at approximately 2 years.</li> </ul>
<p>Improvement in ORR in Study CA209039 with:</p> <ul style="list-style-type: none"> <li>• ORR of 60% in comparable group <ul style="list-style-type: none"> <li>– No with CR= 0/15</li> <li>– No with PR = 9/15</li> </ul> </li> <li>• Estimated median duration of response 12 months (95% CI 1.8, NA)</li> </ul>	<p>Strength:</p> <ul style="list-style-type: none"> <li>• ORR result consistent across the two studies</li> <li>• Estimated median DOR clinically meaningful</li> </ul> <p>Uncertainties:</p> <ul style="list-style-type: none"> <li>• 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</li> <li>• Retrospective analysis of tumour response by IRRC following late protocol amendment</li> <li>• No patient achieved CR.</li> </ul>
<p>Future studies to confirm the results of these early studies</p>	<p>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.</p> <p>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: <i>'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'</i>. Safety data from this DBL has been provided, but no efficacy data.</p>

**Table 15. Second round assessment of benefits**

<b>Indication:</b> <i>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.</i>	
<b>Benefits</b>	<b>Strengths and Uncertainties</b>
<p>There were 5 patients in 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).</p>	<p>Uncertainties:</p> <ul style="list-style-type: none"> <li>· The number of patients described in the dossier is too small to support the proposed indication</li> <li>· There will be no further information available regarding this indication from studies planned by the sponsor.</li> </ul>

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 OS of relapsed or 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.

### **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 DBL 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 above). Table 16 (shown below) however contains updated data and some new information from the sponsor's responses.

**Table 16. Second round assessment of risks**

Risks	Strengths and Uncertainties
<p>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):</p> <p><i>Adverse reactions:</i></p> <ul style="list-style-type: none"> <li>• AEs, all cause, all grades reported in all patients (100%)</li> <li>• Grade 3 or 4 AEs, all cause, reported in 49.5%</li> <li>• SAEs, all cause, reported in 30.5%, with Grade 3 or 4 in 20%</li> <li>• Discontinuations due to AEs in 7 patients (7.4%)</li> </ul> <p><i>Hospitalisation:</i></p> <ul style="list-style-type: none"> <li>• Prolonged hospitalisation in 28% due to SAEs in the cHL SCE group (Cohort B of Study CA209205 + ASCT-bren failed group of Study CA209039)</li> </ul> <p><i>Death:</i></p> <ul style="list-style-type: none"> <li>• Deaths due to nivolumab toxicity reported in one patient (MSOF) (1.25%) although this was changed after database lock.</li> <li>• Narratives of deaths and SAEs suggest that irAEs were under-recognised and under-treated in some patients and may have contributed to deaths.</li> </ul> <p><i>Immune mediated AEs:</i></p> <ul style="list-style-type: none"> <li>• All cause IMAEs (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%).</li> <li>• All cause immune mediated endocrine AEs not requiring immunosuppression: hypothyroidism/thyroiditis (15.8%), adrenal insufficiency (1.1%), hyperthyroidism (1.1%).</li> <li>• The IMAEs of pneumonitis, TEN, SJS, hepatitis, encephalitis, myasthenia gravis, myositis, myocarditis and rhabdomyolysis have each been associated with fatal outcome in patients receiving nivolumab monotherapy.</li> </ul> <p><i>Increased risk of complications of allo-SCT:</i></p> <ul style="list-style-type: none"> <li>• Potential increase in GVHD and other complications in patients having allo-SCT after nivolumab treatment.</li> </ul>	<p>Strengths:</p> <ul style="list-style-type: none"> <li>• Despite the frequency of AEs, there was no apparent effect on average measures of QoL during the Weeks 9 to 33 of treatment</li> <li>• Deaths recognised as resulting from nivolumab toxicity were rare; discontinuations due to AEs were infrequent.</li> </ul> <p>Uncertainties:</p> <ul style="list-style-type: none"> <li>• 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)</li> <li>• 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)</li> <li>• Generalisability of safety results to the wider population outside clinical studies, noting that: <ul style="list-style-type: none"> <li>– patients with ECOG &gt;1 and patients with interstitial lung disease were excluded.</li> <li>– IMARs in some patients in the clinical trials had delayed recognition and management despite specific training and the investigator's brochure.</li> </ul> </li> </ul>

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 DRAEs, 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 IRAEs 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 irARs 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 hourly, 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).

### **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.

### **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.

## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a Risk Management Plan (RMP): EU-RMP version 6 (dated 25 May 2016 with a DLP of 18 December 2015) and Australian Specific Annex (ASA) version 6 (dated 20 September 2016) which was reviewed by the RMP evaluator.

### Safety specification

The sponsor has proposed the following Summary of Safety Concerns shown in Table 22 below. The Summary of Safety Concerns remains unchanged in EU-RMP version 6 from the previous version. However, the Safety Concerns listed in the ASA include specific risks recommended by the RMP Evaluator (with the exception of the inclusion of systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS) and multiple organ failure (MOF)) in the RMP evaluation for the RCC indication. These additions with explanations are footnoted in Table 17 below.

**Table 17. Sponsor's summary of ongoing safety concerns**

Sponsor's summary of ongoing safety concerns	
Important identified risks	Immune related pneumonitis
	Immune related colitis
	Immune related hepatitis
	Immune related nephritis or renal dysfunction
	Immune related endocrinopathies
	Immune related skin adverse reactions <sup>1</sup>
	Immune related neurological adverse events <sup>2</sup>
	Other irARs (including SIRS/MODS/MOF, uveitis, pancreatitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, rhabdomyolysis) <sup>3</sup>
	Severe infusion reactions
Important potential risks	Embryofetal toxicity
	Immunogenicity



Sponsor's summary of ongoing safety concerns	
	Cardiac arrhythmias (previously treated melanoma indication only)
Missing information	Paediatric patients < 18 years of age
	Patients with severe hepatic and/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 <sup>2</sup>

1) Slight alteration in the wording from ASA version 4 (Immune Related Rash and Severe Skin Reactions) to ASA version 6 (Immune related skin adverse reactions). In the EU RMP version 6 this Safety Concern is stated as 'Immune Related Rash.'

2) Safety concerns listed in the ASA and added to include specific risks recommended by the RMP evaluator in the RMP evaluation for the RCC indication.

3) Recommended by the clinical evaluator for the Safety Concerns for nivolumab and the extension of indication (RCC) but at this stage not added to the Safety Concerns by the sponsor in ASA version 6. At the 7 October 2016 ACPM meeting, the Committee considered that there is insufficient evidence to support a precaution about SIRS/MODS/MOF. The ACPM noted that the number of SIRS reviewed by sponsor is insufficient to make a causal linkage and that based on the data available from MODS/MOF cases, these events could be attributed to underlying disease progression rather than nivolumab therapy.

### Pharmacovigilance plan

Additional pharmacovigilance activities have been proposed for the important identified risks, as well as the important potential risk of cardiac arrhythmia and are shown in Table 18 below. No tumour/indication specific changes have been proposed to the Pharmacovigilance section of the ASA since the TGA approved nivolumab ASA version 2.2 (that is, versions 2.2 through 6).

**Table 18. Pharmacovigilance plan**

Safety concern	Additional activity	Proposed actions/outcomes	Planned submission date
<b><i>Ongoing studies (RMP)</i></b>			
Immunogenicity Cardiac arrhythmias (previously treated melanoma indication, only)	Study CA209172: A Phase II, single arm, open label, multicentre clinical trial with nivolumab for subjects with histologically confirmed Stage III (unresectable) or Stage IV melanoma progressing post prior treatment containing an anti-CTLA-4 monoclonal antibody	To further characterise immunogenicity and its impact on efficacy and safety  To evaluate and characterise cardiac arrhythmia risk	4Q 2017



Safety concern	Additional activity	Proposed actions/outcomes	Planned submission date
	Study CA209171: A single arm, open label, multicentre clinical trial with nivolumab monotherapy in subjects with advanced or metastatic SQ NSCLC who have received at least two prior systemic regimens for the treatment of Stage IIIb/IV SQ NSCLC.		4Q 2017
	Study CA209357: A US multisite observational registry in patients with unresectable and metastatic melanoma (observational registry).		Annual reports Ongoing
<b><i>Ongoing studies (ASA)</i></b>			
Immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, neurological ARs, other irARs, and infusion reactions	Clinical trial of nivolumab combined with ipilimumab followed by nivolumab monotherapy as first line therapy of subjects with histologically confirmed Stage III (unresectable) or Stage IV melanoma.  At TGA request, this study is included as an Australian-specific additional pharmacovigilance activity. (Study CA209401)	To characterise high-grade treatment related AEs.  Global study and Australia is a participant.	Q2 2022 (estimated).
Immune related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs , neurological ARs, other irARs, and infusion reactions	Post-marketing pharmacoepidemiology study: pattern of use and safety/effectiveness of nivolumab in routine oncology practice. includes patients with melanoma and NSCLC (Study CA209234).	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab.  Includes Australian patients	Interim annual reports;  Final CSR: 4Q 2024
<b><i>Planned Studies (RMP)</i></b>			
Use in patients who have undergone influenza vaccination.	Study CA20999J: Evaluation of risk of muscle damage in cancer patients on checkpoint inhibitor therapies after receiving influenza vaccination. A nested case-control study using claims data.	No Australian patients	Q4 2018

Safety concern	Additional activity	Proposed actions/outcomes	Planned submission date
Safety of nivolumab in patients with cHL who undergo HCT.	Study CA209835: A registry study in patients who underwent post-nivolumab allogeneic HSCT. The primary objective of this study is to analyse treatment related mortality at 6 months after an allogeneic HCT among patients with cHL who were previously treated with nivolumab, either alone or in combination.	No Australian involvement.  (Draft protocol synopsis in this submission).	Annual update with PSUR starting at DLP 3 July 2017.  Interim CSR submission July 2019.  Final CSR submission 4Q2022

**Table 19. Ongoing efficacy studies**

Study ID	Study description/aim	Final CSR submission
CA209067	Final clinical study report for Study CA209067: A Phase III, randomised, double blind study of overall survival in subjects treated with nivolumab monotherapy, ipilimumab monotherapy, and nivolumab combined with ipilimumab.	31 March 2017
To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (for example, other genomic-based methods/assays, and associated cut-offs, that might prove more sensitive and specific in predicting response to treatment based on PDL1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, expression of components of antigen-presentation complexes and/or other inhibitory checkpoint receptors/ligands within tumour, and so on) as predictive of nivolumab and/or nivolumab + ipilimumab combination therapy efficacy. This will be provided for all the approved indications.		
CA209038, CA209066	Melanoma monotherapy studies	30 September 2017
CA209038, CA209067, CA20906 <sup>a</sup>	Melanoma combination (with ipilimumab) studies	31 March 2019
CA209017, CA209057, CA209026	NSCLC studies	31 March 2018
CA209025, CA209009	RCC studies	31 March 2018
CA209009, CA209038, CA209064	To further investigate the relation between PD-L1 and PDL2 expression in Phase I studies.	31 March 2017
CA209066, CA209057, CA209025	To further investigate the associative analyses between PD-L1 and PD-L2 expression conducted in Studies CA209066, CA209057, and CA209025.	30 June 2018
CA209009, CA209038, CA209064	To further investigate the possible change in PD-L1 status of the tumour during treatment and/or tumour progression in Studies CA209009, CA209038 and CA209064.	30 September 2017

Note: These studies are conditions of the Marketing Authorisation in the EU; a) As reported in the RMP. The sponsor has clarified that this should read Study CA209069 and will correct it in future versions of the RMP.

### **Risk minimisation activities**

Additional risk minimisation activities are planned for the important identified risks: immune related pneumonitis, immune related colitis, immune related hepatitis, immune related nephritis or renal dysfunction, immune related endocrinopathies, immune related skin adverse reactions, immune related neurological adverse events and other irARs.

The additional risk minimisation activities (as per the EU-RMP version 6 and ASA version 6) consist of:

- a Healthcare Professional (HCP) communication tool (irAR Management Guide); and
- a patient communication tool (Patient Alert Card (PAC)), to facilitate safe and effective use of nivolumab in the post-marketing setting.

The sponsor agreed to implement a smaller, streamlined and less complex format for the PAC, and to update the PAC to reflect the revised Summary of Safety Concerns.

The sponsor has provided two simplified PACs in the appendices of ASA version 6, one for monotherapy and one for use in combination with ipilimumab (Yervoy). Both have been simplified and are more suited for consumers. They include reference to the neurological side effects reflecting the immune related neurological adverse events included as an Important Identified Risk in the Summary of Safety Concerns.

The sponsor has committed to providing the TGA the updated versions when available, after finalisation of the PI.

The sponsor has also provided an updated HCP Tool in ASA version 6 which includes the RCC indication and reflects the revised Summary of Safety Concerns. In updating the HCP irAR Management Guide, the sponsor no longer lists specific non-corticosteroid therapy products and make a reference to them in more general terms (for example anti-TNF $\alpha$  agents or to the use of other systemic immunosuppressants). On completion of this application and finalisation of the Opdivo PI, the sponsor commits to provide the updated HCP Tool to the TGA. This should include the cHL indication.

### **Reconciliation of issues outlined in the RMP report**

Table 20 below summarises the RMP evaluator's first round evaluation of the RMP, the sponsor's responses to issues raised and the TGA's evaluation of the sponsor's responses.

**Table 20. Reconciliation of issues outlined in the RMP report**

Reconciliation of issues outlined in the RMP report
<p><b>Recommendation 1:</b> Any safety concerns identified by the clinical evaluator that impact on the safety specifications should be addressed in a revised RMP.</p>
<p><i>Sponsor's response: The sponsor acknowledges the RMP evaluator's request. The only relevant question raised within the Clinical Evaluation Report, on the safety with subsequent allogeneic stem cell transplant has been addressed in the Response to Clinical Evaluation Report. Further, 2 specific Questions on the RMP have been raised by the Clinical Evaluator and sponsor's Responses to the RMP related questions in the Clinical Evaluation Report are provided in the Response to Clinical Evaluation Report.</i></p>
<p><b>RMP evaluator comment:</b> Study CA209835, a registry study in patients who underwent post-nivolumab allo-HSCT has been included in the pharmacovigilance plan to address the above issue. Inclusion of this safety concern in the ASA is recommended.</p>
<p><b>Recommendation 2:</b> The safety concern 'immune related rash' in the RMP should be amended in the next version of the RMP to read 'immune related skin adverse reactions' as per ASA version 6.</p>
<p><i>Sponsor's response: The sponsor confirms that the nivolumab EU-RMP version 5.6 submitted with this response has listed this safety concern as 'immune related skin adverse reactions'.</i></p>
<p><b>RMP evaluator comment:</b> The terminology used in the EU-RMP and ASA has been amended as requested, and the terminology has also been updated in the irAR Management Guide.</p>
<p><b>Recommendation 3:</b> Include the planned date of submission of Study CA209401 in the ASA when next updated.</p>
<p><i>Sponsor's response: The sponsor does not agree with including planned submission dates in the ASA, as these are subject to change. As per the response to the second round RCC RMP evaluation report a final study report for Study CA209401 is due in Q2 2022 (estimated) and the sponsor agrees to submit the final report to the TGA. Any new safety information emerging from Study CA209401 will be reported to the TGA in accordance with the TGA pharmacovigilance regulations (Australian Requirements and Recommendations for Pharmacovigilance Responsibilities of Sponsors of Medicines, version 1.3, June 2014).</i></p>
<p><b>RMP evaluator comment:</b> The estimated due date has been noted in the RMP Evaluation Report.</p>

Reconciliation of issues outlined in the RMP report
<p><b>Recommendation 4:</b> The status of Study CA209234 should be updated in the EU-RMP to indicate that it is currently ongoing. The sponsor should also amend the number of Study CA209069 in the future version of the RMP.</p>
<p><i>Sponsor's response: These updates are reflected in the nivolumab EU-RMP version 5.6 submitted with this response.</i></p>
<p><b>RMP evaluator comment:</b> The RMP has been amended.</p>
<p><b>Recommendation 5:</b> The sponsor should include the cHL indication in the updated HCP Tool and submit when available to the TGA.</p>
<p><i>Sponsor's response: The HCP Tool is intended to focus primarily on the irARs and their management. The sponsor has a large number of potential indications planned and wishes to reduce the burden of version management for HCPs. As discussed and agreed with the TGA on 24 November 2016, the sponsor plans to remove the indications from the HCP Tool. The HCP Tool will, however, include a reference to the most recent Australian PI.</i></p>
<p><b>RMP evaluator comment:</b> The sponsor's response is satisfactory as discussed and agreed by teleconference with the RMP Evaluation Section.</p>

### Summary of recommendations

The following new or outstanding issues should be addressed by the sponsor:

*Recommendation 1:* The sponsor should add 'Complications of allogeneic HSCT following nivolumab therapy' as an Important Potential Risk to the ASA for consistency with the RMP. Routine (for example, the PI statement proposed by the clinical evaluator) and additional risk minimisation activities should also be assigned (consistent with those in EU-RMP version 5.6).

*Recommendation 2:* The sponsor should add the potential risk of 'Complications including acute graft versus host disease and transplant-related mortality of allogeneic haematopoietic stem cell transplant following nivolumab therapy' to the irAR Management Guide, consistent with the additional risk minimisation activities in the RMP, and submit it to the TGA for review prior to registration. In the EU, this Guide is called an Adverse Management Guide rather than an irAR Guide. It would be acceptable to update the title of the Australian materials in a similar way.

*Recommendation 3:* The sponsor should prominently display the internet address for the full PI on the sponsor's additional risk minimisation documents (the pack insert, the PAC, and the irAR Management Guide). This will ensure that clinicians are able to easily locate and refer to the full PI as per the clinical evaluator's recommendation.

*Recommendation 4:* The sponsor should clarify if it still intends to undertake additional pharmacovigilance activity in the form of data analysis, to address the missing information regarding the potential effect of influenza vaccine on the safety of nivolumab (included in EU-RMP 4.5 and ASA version 6.0 but not EU-RMP 5.6) or if this has been superseded by inclusion of Study CA20999J (added in EU-RMP version 5.6).

*Recommendation 5:* The sponsor should ensure that changes made to EU-RMP version 5.6 and ASA version 7.0 are incorporated into subsequent versions of RMP/ASA when they are created.

**Proposed wording for conditions of registration**

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

*'Implement EU-RMP (version 5.6, dated 9 November 2016, data lock point 26 May 2016) with Australian Specific Annex (version 7.0, dated 21 December 2016), submitted with application PM-2016-00712-1-4, and any future updates as a condition of registration.'*

**VI. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate's overview and recommendations:

**Quality**

There was no requirement for a quality evaluation in a submission of this type.

**Nonclinical**

There was no requirement for a nonclinical evaluation in a submission of this type.

**Clinical**

The CER refers to 'overall response rate' in some sections, while this overview refers to 'objective response rate'. The clinical dossier included:

- Interim CSRs for the Phase II Study CA209205 and Phase I Study CA209039
- An Integrated Summary of Safety in which safety data from these studies were compared to nivolumab safety data from solid organ tumours (RCC, melanoma, NSCLC)
- PPK and exposure-response analyses of nivolumab in treatment of CHL patients.

The CER provided a detailed examination of the available data and discussion of issues and is available in Attachment 2. Following is a summary of the findings of the clinical evaluator and unresolved issues.

**Pharmacology*****Pharmacokinetics***

Serum nivolumab measurements using a sparse sampling model were obtained for both Studies CA209205 and CA209039.

Results were combined with data from other studies to develop the PPK model and exposure-response analyses.

The dose proposed for nivolumab monotherapy is 3 mg/kg administered intravenously over 60 minutes every 2 weeks, as for other tumour types. Pharmacokinetics has been

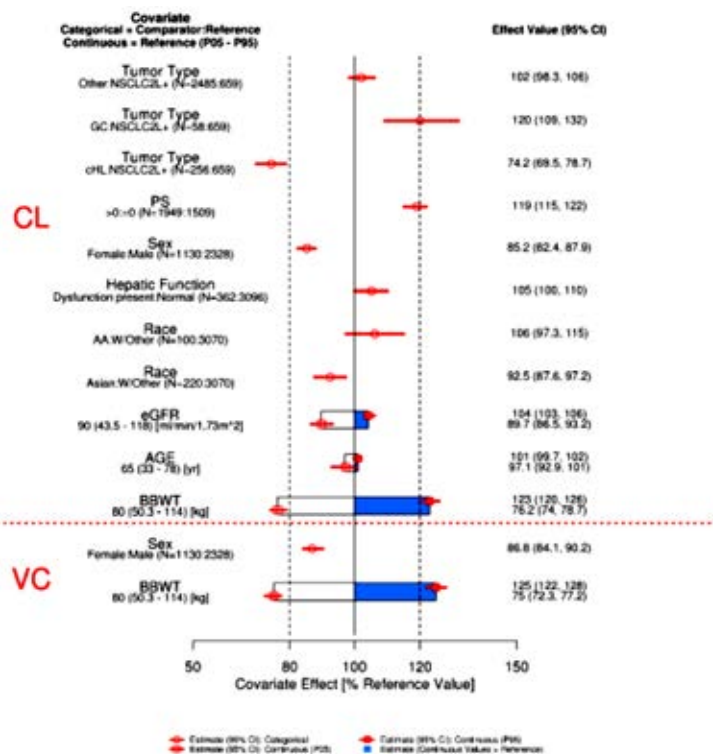
documented in patients with different types of solid tumours including NSCLC, melanoma, RCC (see PK section of current PI).

The evaluator noted steady state was not reached in cHL until Week 20 (compared with Week 12 in solid tumours) but inter-individual variability as estimated by the coefficient of variation of geometric means for the maximum serum concentration and area under the concentration-time curve from 0 to 336 hours was < 30% and consistent with that seen in solid tumours.

### PPK analyses

Updated PPK modelling using a model in which CL decreased with time was provided with the sponsor's response to TGA questions response as shown in Figure 4 below. It suggests that in patients with cHL nivolumab clearance was approximately 26% reduced compared to patients with NSCLC2L and other solid tumours, with 39% greater exposure.

**Figure 4. Covariate effects on PK model parameters (full PPK model)**



Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

Note 2: Continuous covariate effects (95% CI) at the 50/95th percentiles of the covariate are represented by the end of horizontal lines (horizontal lines). Open/shaded area of boxes represent the range of covariate effects from the median to the 50/95th percentile of the covariate.

CL = clearance, VC = volume of central compartment.

### Pharmacodynamic data

Studies CA209039 and CA209205 both provided pharmacodynamic data on PD-L1 expression on R-S cells and 9p24.1 chromosomal abnormality from a small number of patients.

Immunogenicity was also examined by the evaluator under pharmacodynamics.

### Exposure-response analyses

There was minimal difference (3%) in predicted OR for a subject with  $C_{avg,ss}$  at the ninety-fifth percentile (161.9  $\mu\text{g/mL}$ ) compared to a subject at the median  $C_{avg,ss}$  suggesting a flat range for OR in the exposure-response curve at higher concentrations.



Exposure, as measured by  $C_{avg,ss}$ , was not assessed as a significant predictor of Grade 3+ DRAEs; the hazard ratio coefficient was 0.7949 (95% CI 0.2219, 2.847).

The increased nivolumab exposure in cHL patients relative to solid tumour patients was considered by the sponsor unlikely to be clinically relevant in the cHL population. However the evaluator noted that reliability of exposure-response modelling for cHL treatment was limited by brief duration of dosing for some subjects and the same dosing regimen across subjects.

*Unresolved issue identified by clinical evaluator*

The clinical evaluator considered that a potential clinically meaningful effect of increased exposure cannot be excluded.

## **Efficacy**

Efficacy in cHL is claimed based on the results described in the interim CSRs for Phase II Study CA209205 and for Phase I Study CA209039, in a total of 103 patients.

### **Study CA209205**

*Design and methodology*

This Phase II single arm open label study included patients > 18 years, ECOG performance status  $\leq 1$  with relapsed/refractory cHL and measurable disease, who had failed ASCT. Biopsy confirmation of cHL prior to initiation of study drug was required. Patients with prior allogeneic SCT or CNS lymphoma were excluded (see Attachment 2 for full study design and inclusion/exclusion criteria).

Cohort B included 80 patients who had received brentuximab vedotin treatment as salvage following failure of ASCT. This was the only cohort with efficacy results.

The primary outcome measure was ORR according to IRRC, using 2007 IWG criteria; defined as proportion of subjects achieving the BOR of either PR or CR. 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. Each patient had regularly scheduled scans (CT/MRI and PET) for tumour response assessment, at Weeks 9, 17, 25, 37 and 49 (CT), and 17, 25 (PET), with additional PET for confirm CR. BOR was allocated to the highest category observed for any time-point response for each patient. Minimum duration of follow-up was 6 months for the interim analyses initially presented in the submission, with DBL 20 August 2015. This was changed from 12 months with a late protocol amendment.

Secondary outcome measures included DOR, CR, PR rates, and health-related QoL as assessed by EORTC-QLQ-C30 questionnaire version 3.

Exploratory endpoints included PFS per IRRC, and OS.

*Patient group*

Median age in Cohort B was 37 years; 89% were White, 64% male, 67.5% Stage IV disease at study entry, 92.5% with lesions in lymph nodes, 27.5% in lung; 45% extralymphatic involvement, bone marrow involvement 10%, and 22.5% had B symptoms at Baseline. The median number of doses administered in Cohort B was 17 (range 3 to 25); 76% received > 90% of planned dose intensity. See Attachment 2 for discontinuations at initial DBL. 10 subjects had systemic therapy, 5 proceeded to allo-SCT and one to ASCT.

*Efficacy results*

At the October 2015 DBL; as per the interim CSRs initially submitted, with median follow-up 8.92 months:



- The primary efficacy variable was ORR as per IRRC:
  - ORR (95% CI): 53/80, 66.3% (54.8, 76.4)
  - based on the BOR of CR (95% CI): 7/80, 8.8% (3.6, 17.2)
  - CR + PR (95% CI): 46/80, 57.5% (45.9, 68.5).
- SD was reported for 18 subjects (22.5%), relapsed or progressive disease (PD) in 6 subjects, and BOR could not be determined in 3 subjects.

#### Other variables

- DOR:
  - DOR median (95% CI): 7.8 months (6.6, NA), range 0.0+, 9.5+
  - DOR is immature due to censoring, with 31/53 responders per IRRC still on treatment and censored prior to the median.
- Time to Response: 31 of the 53 (58.5%) responders achieved their response by the time of first scan (9 weeks). Median time to CR and PR was 4.44 (range 3.3 to 6.9) and 2.10 (1.6 to 5.7) months, respectively.
- The median PFS per IRRC was estimated at about 10 months (95% CI: 8.41, NA); at median follow-up of 8.9 months and with 24 events (23 progression and 1 death), due to the number censored (56/80) this was considered 'unstable'.
- Other outcome measures are shown in Attachment 2. The ORR was 66.7% in subjects with PD-L1  $\geq$  1% expression (n = 34 PR, n = 4 CR), 83.3% in subjects with PD-L1 < 1% (n = 5 PR), and 58.5% in those without a quantifiable PD-L1 (n = 7 PR, n = 3 CR).

Of the 18/80 patients with B symptoms at Baseline, 16 had resolution of symptoms. The SCE stated '*No clinically meaningful deterioration was observed in any of the EORTC QLQ-C30*'; the evaluator commented that while interpretation was difficult, it was consistent with the results of EQ-5D VAS, and suggested QoL was not worsened in most patients.

Table 21 below gives the results as initially submitted; no updated data were provided.

**Table 21. ORR after median follow-up of 23.3 months**

Efficacy parameter	Result per IRRC		Result per Investigator	
	All patients (n = 23)	ASCT-Bren Failed group (n = 15)	All patients (n = 23)	ASCT-Bren Failed group (n = 15)
ORR (CR + PR/total)	61%	60%	87%	87%
Number with CR	3	0	5	2
Number with PR	11	9	15	11
Number with SD	7	5	3	2

The K-M estimate of median DOR per IRRC:

- 12 months (95% CI 1.8, NA) for the ASCT-bren failed group
- This was not reached for all cHL subjects.

Subjects with ongoing disease control (ongoing CR, PR, or SD) entered the first follow-up period and no longer received study drug; assessments were continued for 1 year. At the time of the CSR, 3 patients remained on treatment (investigator response PR), 13 were in follow-up, 5 had died, and 2 were lost to follow-up. Four had CR, and 2 completed the maximum of 2 years of treatment. The median number of cycles was 18 (range 6 to 48). Almost half the subjects had at least one dose delay (11/23) but none were due to haematological toxicity. Discontinuations reported were due to disease progression (n = 6, 5 in the ASCT-bren failed group), drug toxicity (n = 2, pancreatitis and MDS both in the ASCT-bren failed group), other reasons (n = 4, 'bone marrow transplant' or SCT), and subject request (n = 2, allogenic SCT, joint and muscle pain).

Based on the IRRC assessment of PFS, the K-M estimate of median PFS for the ASCT-bren failed group was 12.7 months (95% CI 5.91, NA) and not reached for all cHL subjects. At the time of DBL for this interim CSR, with median follow-up of 23 months (range 7 to 28 months), 5 patients had died, 4 from the ASCT-bren failed group (26.7%). Estimated median OS was not reached for cHL all subjects or ASCT-bren failed subgroup.

Of the 5 patients with no prior ASCT, 4 had an objective response to nivolumab (one CR with DOR of 24 months; 2 ceased to undergo ASCT; one ceased due to disease progression and went on to treatment with brentuximab vedotin and radiotherapy).

### ***Integrated Summary of Efficacy***

The sponsor's Integrated Summary of Efficacy was based on 80 subjects from Cohort B in Study CA209205 and 15 subjects from Study CA209039 who had prior brentuximab vedotin treatment after failure of ASCT. The ORR (95% CI) derived was 65.3% (54.8 to 74.7), consistent with biological activity with potentially important clinical efficacy. Discrepancies between studies included different durations of follow-up, different definitions of BOR, and different criteria for ceasing treatment.

### ***Efficacy issues identified as unresolved by the clinical evaluator***

- The evaluator recommended removal of the second part of the proposed indication, due to insufficient data on use of nivolumab monotherapy in patients who are ineligible for ASCT
- The evaluator noted that data from a subsequent DBL in June 2016 had not been used to provide updated efficacy analysis, and recommended provision of follow-up reports for Studies CA209205 and CA209039
- The evaluator recommended changes to the product documentation.

### ***Delegate's conclusions on efficacy***

The studies provided were small and without comparator arms. The ORR was 60% or more in the target cHL population. The ORR for brentuximab vedotin was around 75% in cHL CD30+ patients post-ASCT. The ORR for nivolumab compares favourably to available historical data for other single agents used for cHL.

It is reasonable to expect that the nivolumab ORR results predict meaningful clinical efficacy in patients who receive brentuximab treatment as salvage following failure of ASCT. Data from 5 patients in Phase I Study CA209039 are insufficient to support the use of nivolumab monotherapy in patients who are not candidates for ASCT.

The limitations of the evidence should be clearly stated as part of the indication and the trial data should be accurately described in the PI.

The final CSRs for the studies provided in the dossier should be provided to TGA.

## Safety

The safety profile of nivolumab in cHL treatment was considered by the sponsor to be consistent with prior data in studies of patients with solid tumours. The clinical evaluator summarised AE data from 3 datasets and 2 DBLs (available in Attachment 2) and is reproduced below in Table 22. The SCE population is the target group with relapsed or refractory cHL who have failed treatment with ASCT and brentuximab.

**Table 22. Summary of Safety, June 2016 DBL and February 2016 DBL**

	All cHL (Cohort A, B + C of Study CA209205; and Study CA209039) June 2016 DBL	SCE population June 2016	All cHL (Cohort A, B + C of Study CA209205; and Study CA209039) Feb 2016 DBL
	N = 266	N = 95	N = 263
Median duration of therapy in months (range)	18.63 (0 to 23.4)	13.8 (1.1 to 23.4)	NA
Total subjects with an event (%)			
All Cause, all grades 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 <sup>a</sup> (0.4)
a) 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-DBL.			

See Attachment 2 for reports of deaths. The evaluator considered that it was not possible to exclude a contribution of IRAEs secondary to nivolumab to some of these.

The evaluator collated data into a table comparing tumour types and different cHL datasets (available in Attachment 2). There was a longer median duration of therapy for the cHL population; 18.6 months in the SCS (all cHL) population and 12 to 13 months for the target cHL population (SCE) compared to less than 6 months from the melanoma, NSCLC and RCC data. The numbers were markedly smaller from the cHL datasets. DRAEs were somewhat higher in the cHL SCE group (AEs all grade: 90.5%, Grade 3 or 4: 28%) compared to solid tumour types (AEs all grade: 70 to 80%; Grade 3 or 4: 11 to 19%). Of

the most frequently reported AEs, pyrexia and diarrhoea had notably increased frequency in cHL SCE dataset compared to solid tumours.

The evaluator examined IMAEs in detail (see Attachment 2) and considered regulatory impact of these events. The evaluator constructed a table from source data provided by the sponsor. In general the rates of IRAEs reported in the SCS population (all cHL) are lower than those in the SCE population (Cohort B of Study CA209205 and the ASCT-bren failed group from Study CA209039). It is not clear if this is the effect of smaller numbers.

The sponsor stated that while non-clinical models raised the possibility that blockade of PD-1/PD-L1 may enhance GVHD, the rates of clinical transplant-related mortality and acute GVHD were consistent with the historical literature for this cHL patient population. The sponsor confirmed that results from registry study in patients with allogeneic HSCT will be provided in a report when available.

#### ***Safety issues identified as unresolved by evaluator included***

- Analysis provided by the sponsor does not exclude the potential risk of increased GVHD and other complication in patients who receive allo-SCT following nivolumab therapy. Both the FDA and the EMA have included precautions and warnings about this in their PI equivalents, and it should be included in the PI.
- The possibility that increased drug-related AEs and SAEs may occur in cHL patients compared to patients with solid tumours cannot be excluded. There are discrepancies between the total cHL populations, the cHL SCE population, and patients with solid tumours.
- Patient impact of AEs: Updated data indicated that 28% of the cHL SCE population required prolonged hospitalisation due to SAEs. The evaluator considered that elderly patients had a higher risk of serious adverse events including death.
- The online location of the full PI should be included in the pack insert and other documentation.

#### **Delegate conclusions on safety**

There is a limited exposure database for the cHL indication. The clinical evaluator suggested that higher frequency of some AEs in the targeted population with cHL, compared to those seen in solid tumours, could not be excluded. However the proposed PI pools all adverse reaction data.

A new safety issue is the possible increased risk of transplant-related complications of allogeneic-HSCT following nivolumab treatment.

Frequent monitoring for and early treatment of IRARs are part of standard clinical practice with nivolumab treatment. The safety issues raised are not such as to preclude the extension of indications to treatment of adult patients with relapsed or refractory cHL after ASCT and treatment with brentuximab vedotin, but adequate information should be provided in the PI.

The PBRER to January 2017 should be provided as soon as it is available, to ensure all safety issues are updated adequately.

It is recommended that a suitable means of directing the reader to the full PI is included on all product documentation.

#### **Clinical evaluator's recommendation**

The clinical evaluator's conclusion was that Opdivo (nivolumab) could be approved for the 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.'*

The clinical evaluator's recommendation for approval was contingent upon:

- changes to the indication and PI being adopted as recommended by the evaluator
- updated PFS and OS analysis Study CA209039; updated efficacy results for Cohort B; and efficacy results for Cohorts A and C from Study CA209205 being provided to the TGA.

## **Risk management plan**

EU-RMP version 5.6 and ASA version 5.0 were the most relevant versions evaluated for the cHL indication; ASA version 7.0 is the most recent at the time of this overview.

Study CA209835, a registry study in post-nivolumab patients receiving allogeneic HSCT, has been included in the pharmacovigilance plan. Inclusion in the ASA and the irAR Management Guide of safety concern 'complications of allogeneic HSCT following nivolumab therapy' was recommended. As of 2 March 2017, the sponsor has notified TGA of the intention to add this potential risk to an updated ASA (version 8.0).

Additional risk minimisation activities (EU-RMP version 6 and ASA version 7):

- A HCP communication tool (Immune-Related Adverse Reaction (irAR) Management Guide), and
- a PAC (Patient Alert Card), to facilitate safe and effective use of nivolumab in the post-marketing setting.

The sponsor plans to remove the indications from the irAR Management Guide, but include a reference to the most recent Australian PI. The proposed PAC and irAR Management Guide were provided at Appendices 1 and 2 to ASA version 7.0.

## **Wording for conditions of registration**

The suggested wording is: *Implement EU-RMP (version 5.6, dated 9 November 2016, data lock point 26 May 2016) with Australian Specific Annex (version 7.0, dated 21 December 2016), submitted with application PM-2016-00712-1-4, and any future updates as a condition of registration.*

## **Risk-benefit analysis**

### **Delegate's considerations**

There is little regulatory guidance for the use of early phase or exploratory studies, rather than Phase III pivotal studies, as the basis for current approval in Australia.

The TGA-adopted EMA 'Guideline on the evaluation of anticancer medicinal products in man' acknowledges 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'.<sup>18</sup> The guideline notes that a 'small, randomised, reference controlled study' or 'a within-patient time-to-progression (TTP)/PFS analysis (or the combination)' with TTP on last prior therapy compared with time to progression or death on the experimental therapy 'might be a better alternative.' External (including historical) controls are noted 'where the treatment effect is dramatic and the usual course of the disease highly predictable'.

The EMA 'Guideline on clinical trials in small populations' notes that surrogate markers cannot serve as final proof of clinical efficacy or long-term benefit.<sup>19</sup>

FDA guidance mentions objective response rates as a surrogate endpoint reasonably likely to predict a clinical benefit and that a significant rate of durable complete response could provide potentially useful additional evidence.<sup>20</sup>

The ORR of 60% derived from the available data, with median duration of response more than 12 months, suggest that a meaningful clinical benefit is likely for patients who relapse or have recurrence of cHL following ASCT and brentuximab vedotin treatment. Furthermore, the product is registered in Australia for other indications and has pharmacovigilance and risk minimisation systems in place.

However the results are not sufficient to show overall survival benefit in cHL. No confirmatory Phase III studies are planned for the specific indication proposed. The justification provided by the sponsor is that the indication proposed is very narrow, recruitment of a sufficient number of patients for an adequate Phase III study is not possible, and there is no registered treatment for a comparator arm.

The sponsor states that a Phase III trial is planned, to include patients with relapsed/refractory cHL after failure of or ineligibility for ASCT; co-primary endpoints will be complete response rate/complete metabolic response rate and PFS, for the combination of brentuximab + nivolumab compared with single agent brentuximab.

The exposure and safety profile in cHL might vary from that in solid tumours, based on the data evaluated. The most recent PBRER should be provided, and the PI should reflect any differences.

As the risk minimisation activities (such as pack insert, HCP irAR Management Tool, and the PAC) refer to the approved PI, the online location of the full PI (as published on TGA website) should be included on all such documents. Other means of facilitating access should be considered.

### Summary of issues

- The PK profile derived from PPK analyses appears different for cHL compared to solid tumours; clearance was decreased 26% compared to NSCLC 2L+ patients, with 39% higher exposure in cHL.
- Phase I and Phase II interim clinical trial data are available as evidence of safety and efficacy for nivolumab in the treatment of cHL. The sponsor states that no confirmatory Phase III trials will be conducted for the population as specified in the proposed indication.

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<sup>18</sup> EMA/CHMP/205/95/Rev.4: Guideline on the evaluation of anticancer medicinal products in man. Replaces: CPMP/EWP/205/95/Rev.3/Corr (Adopted by TGA June 2006); effective: 1 April 2014.

<sup>19</sup> EMA/CHMP/EWP/83561/2005: Guideline on Clinical Trials in Small Populations. Effective: December 2006.

<sup>20</sup> Guidance for Industry: FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products. December 1998.

- IMARs are known risks. Some AE rates were increased in cHL compared to solid tumours. A newly identified potential risk following nivolumab therapy is risk of complications after subsequent allo-SCT.

### **Proposed action**

The Delegate had no reason to say, at the time, that the application for extension of indications for Opdivo should not be approved for registration, provided that additional qualifying text is included in the indication to specify the limited evidence, and that the PI contains adequate efficacy and safety information for the proposed cHL indication.

### **Request for ACM advice**

The committee is requested to provide advice on the following issues:

1. Are there any implications from the PK modelling for clinical usage and precautions? Is this aspect of the proposed PI adequate?
2. Efficacy: What are the views of the committee on the adequacy of the submitted interim study reports from Phase I and II trials and updated data as support for registration for the cHL indication. Is the notation about limitation of data adequate? Should the indication wording specify adult patients?
3. Safety: Is the available information sufficient for the anticipated clinical setting? Is the proposed PI/CMI with pooled safety data across all indications, and other clinical information, adequate in this regard?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

### **Response from sponsor**

The sponsor welcomes the Delegate's and clinical evaluator's conclusion that Opdivo can be approved for an indication in cHL subject to agreed modifications to the indication and PI.

The sponsor agrees to the inclusion of a note to the indication statement to clarify the basis of approval. However, the proposed note to the indication from the clinical evaluator is not an accurate reflection of the status of the data. Until mature data on PFS and OS are available it is too early to say that PFS and OS improvements have not been demonstrated from these studies. The sponsor recommends that a more accurate statement would be to say that data on PFS and OS are immature.

The nivolumab safety profile is well characterised and has been shown to be consistent over time and across tumours. Data from an integrated population of cHL patients demonstrates that the type, frequency, and severity of AEs were similar to other tumour types (RCC, melanoma, and NSCLC). The PI contains clear information regarding the importance of continuous monitoring of all patients regarding early identification and intervention for adverse reactions. Furthermore, in response to the TGA's request, text on the complications of allogeneic HSCT following nivolumab therapy has been added to the 'Precautions and Adverse Effects' sections of the PI as well as inclusion into the Australian HCP risk management tool for nivolumab. The sponsor agrees with the Delegate that the safety issues raised by the clinical evaluator do not preclude approval of this extension of indication.

The sponsor recognises the recommendations from the Delegate and clinical evaluator on the proposed indication and has amended the proposed indication statement as follows:



*'Opdivo, as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant and treatment with brentuximab vedotin.*

*Note to cHL indication: The approval of this indication is based on overall response rate. Data on progression free survival and overall survival are immature.'*

Nivolumab has been approved for the treatment of relapsed or refractory cHL in the US (17 May 2016), EU (22 November 2016), Switzerland (22 December 2016) and Japan (2 December 2016).

### **Introduction**

In Australia, cHL is a rare disease with high unmet clinical need. The 2013 incidence/2014 mortality rates for HL in Australia were 611 and 94, respectively. The age- adjusted incidence rate for this period is 2.6/100,000 population.<sup>21</sup>

Heavily pre-treated patients with cHL who have failed ASCT and brentuximab vedotin represent an area of substantial unmet medical need as their overall prognosis is poor with a median survival of less than 1 to 2 years. The standard of care for patients with relapsed and refractory cHL is intensive salvage chemotherapy followed by ASCT, which can produce long-term remissions in approximately 50% of patients. The remaining 50% of ASCT patients do not experience long-term disease control with median OS of approximately 27 months.<sup>22</sup> In particular, the prognosis remains exceedingly poor for patients who experience relapse or progressive cHL within one year after ASCT where the median survival time is approximately 1.2 years.<sup>23</sup> New agents that have meaningful clinical efficacy are urgently required to address this medical need for Australian patients. There are no Australian specific treatment guidelines for the treatment of cHL, however, Australian haematologists tend to refer to international guidelines such as those of the National Comprehensive Cancer Network (NCCN) to help inform the development of institutional protocols. The NCCN guideline currently includes nivolumab as an additional therapy option for cHL.<sup>24</sup>

### **Responses to questions raised by the TGA Delegate in the Request for ACM Advice**

#### **Question 1**

*'Are there any implications from the PK modelling for clinical usage and precautions? Is this aspect of the proposed PI adequate?'*

As described in the submission although nivolumab clearance in cHL subjects is 32% lower relative to NSCLC subjects, this 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 Grade 3 or 4 DRAEs. 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 and therefore 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.

<sup>21</sup> Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101. Cat. no. CAN 100. Canberra: AIHW.

<sup>22</sup> Crump M. Management of Hodgkin Lymphoma in relapse after autologous stem cell transplant. Haematology Am Soc Haematol Educ Program 2008;326-33.

<sup>23</sup> von Tresckow B et al. Outcome and risk factors of patients with Hodgkin Lymphoma who relapse or progress after autologous stem cell transplant. Leuk Lymphoma 2014;55(8):1922-4.

<sup>24</sup> NCCN clinical practice guidelines: Hodgkin's Lymphoma. Version 1 2017.

The sponsor agrees with the Delegate's additions to the PI to describe the higher exposure which is not clinically meaningful. Proposed modifications from the sponsor to the 'Pharmacokinetics' section of the PI are summarised below:

*'The pharmacokinetics (PK) of nivolumab is linear in the dose range of 0.1 to 10 mg/kg. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.'*

*Based on a population PK analysis, using data predominantly from patients with melanoma, NSCLC and RCC, the geometric mean clearance (CL), terminal half-life, and average exposure at steady state at 3 mg/kg every 2 weeks of nivolumab were 9.5 mL/h, 26.7 days, and 75.3 µg/mL, respectively.*

*Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold.*

*In patients with cHL, nivolumab clearance was lower resulting in a 15 day increase in the half life and a 43% increase in exposure (as measured by median  $C_{avg,ss}$ ). The lower nivolumab clearance was not considered clinically meaningful; there was a flat predicted exposure-response relationship.'*

This recommendation for the PI is made on the basis that the nivolumab exposure-response relationship for efficacy was relatively flat in cHL patients. Furthermore, clinically meaningful responses (ORR of 65.3% by IRRC assessment) with the 3 mg/kg dose were demonstrated in cHL and most importantly, higher nivolumab exposures have not been shown to be a significant predictor of the risk of Grade 3 or 4 DRAEs. Indeed, data presented in the application describe that Grade 3 or 4 AEs were reported less frequently in cHL (30.0%) compared with RCC (53.2%), melanoma (40.5%), and NSCLC (45.6%).

#### Question 2

*'Efficacy: What are the views of the committee on the adequacy of the submitted interim study reports from Phase I and II trials and updated data as support for registration for the cHL indication. Is the notation about limitation of data adequate? Should the indication wording specify adult patients?'*

Efficacy data to support the proposed indication in cHL is based on data derived from two studies: Study CA209205 (Phase II, 80 subjects) and Study CA209039 (Phase I, 15 subjects). Both IRRC and investigators assessments demonstrated compelling anti-tumour activity with nivolumab treatment which resulted in a high rate of durable objective response. The sponsor believes that this is convincing evidence in the context of the proposed indication, where there is a very high unmet clinical need in a small patient population with relapsed or refractory cHL who have already received ASCT and brentuximab, and who have no other approved treatment options.

Based on the most recent data submitted to TGA for Study CA209205 Cohort B (April 2016 DLB), after a minimum follow-up of 12 months (median follow-up of 15.44 months), the ORR by IRRC was 67.5% (95% CI: 56.1, 77.6) and the median DOR per IRRC was 13.14 months (95% CI: 8.74, NA).

Although the sponsor acknowledges that PFS and OS were exploratory endpoints and that the data for PFS and OS continues to mature, the PFS and OS results to date on the use of nivolumab post-ASCT and brentuximab failure provide relevant clinical outcomes in an advanced cHL population with high unmet medical need. In Study CA209205 Cohort B at the time of DBL in April 2016, the median PFS was 14.8 months (95% CI: 11.3, NA) with a PFS rate at 12 months of 55% (95% CI 41, 66), whilst the median OS had not been reached with a 12 month OS rate of 95% (95% CI 87, 98).

The sponsor agrees with the Delegate's conclusion that *'the ORR for nivolumab compares favourably to available historical data for other single agents used for cHL'*. It should be

noted that compared with the historical control data, the intended patient population for this submission consists of more heavily pre-treated patients who had failed both ASCT and brentuximab therapy. It is also clinically noteworthy that the durability of responses consistently favoured nivolumab over historical controls.

The sponsor recognises the recommendations from the Delegate and clinical evaluator on the proposed indication. In response:

- The sponsor agrees that the indication wording should specify adult patients;
- The sponsor agrees to remove the part of the indication which has sought the use of nivolumab in patients ineligible for ASCT based on the limited data in Study CA209039;
- The sponsor agrees to the inclusion of a note to the indication statement to clarify the basis of approval. Specifically, the sponsor proposes the changes to the indication [as given above at the start sponsor's response].

The sponsor deems that the version of the note to the indication proposed by the clinical evaluator which states that '*an improvement in progression free survival or overall survival has not been demonstrated*' is not an accurate reflection of the status of the data. In Studies CA209205 and CA209039, PFS and OS continues to evolve as the duration of follow-up has not yet been sufficient for a median OS to be reached. Until mature data on PFS and OS are available it is too early to say that PFS and OS improvements have not been demonstrated from these studies. The sponsor recommends that a more accurate statement would be to say that data on PFS and OS are immature. The sponsor is agreeable to submitting the final CSRs for Studies CA209205 and CA209039 to the TGA.

### Question 3

*'Safety: Is the available information sufficient for the anticipated clinical setting? Is the proposed PI/CMI with pooled safety data across all indications, and other clinical information, adequate in this regard?'*

The sponsor agrees with the Delegate that the safety issues raised by the clinical evaluator do not preclude approval of this extension of indication. The nivolumab safety profile is well characterised and has been shown to be consistent over time and across tumours. The PI has clear information regarding the importance of continuous monitoring of patients and early identification of immune-related adverse drug reactions and provides recommendations for interventions and dose modifications for the management of these potential effects. On 27 February 2017, a PBRER for the period 4 July 2016 through 3 January 2017 was submitted to the TGA. The conclusion from the PBRER was that a comprehensive and detailed review of all safety and efficacy data/information received during the reporting period for nivolumab did not reveal any safety concern that significantly changed the established positive benefit-risk balance of nivolumab for the adult treatment of advanced (unresectable or metastatic) melanoma, locally advanced or metastatic NSCLC after prior chemotherapy, advanced RCC after prior therapy, relapsed or refractory cHL, recurrent or metastatic squamous cell carcinoma of the head and neck after platinum based therapy, and the ongoing evaluation of nivolumab in additional indications and tumour types.

*Safety of nivolumab in cHL:* In order to characterise the safety profile of nivolumab monotherapy in patients with cHL, safety data from Study CA209205 (Cohort A + B + C; n = 240) and Study CA209039 (all cHL, n = 23) were integrated into a single analysis population (n = 263 subjects), here to described as the SCS population. While the studies/cohorts are different in size and length of follow up, all of these cHL patients received the same nivolumab dose. The integrated SCS population enables assessment of lower frequency events and provides the best opportunity to increase the precision of AE rates and provide a more clinically accurate representation of the overall adverse reaction

profile of nivolumab in cHL. For this reason, the sponsor presented the SCS population as the primary population for safety in the application and contends that since the SCE population is more limited for assessing safety (n = 95), that the SCS population is a more reliable dataset to draw conclusions from.

Data from the SCS population in cHL demonstrates that the type, frequency, and severity of AEs were similar to other tumour types (RCC, melanoma, and NSCLC). Although the duration of exposure was longer in cHL treated patients, the exposure adjusted AE incidence rates (events per 100 person years of exposure) were 1652.6 in cHL and 1648.7, 1747.5, and 1795.6 in RCC, melanoma, and NSCLC, respectively. Therefore, the sponsor has concluded that the safety profile of nivolumab monotherapy in cHL was consistent with the safety profiles of nivolumab monotherapy in other tumour types (RCC, melanoma, and NSCLC).

Thus, the sponsor believes that the benefit-risk assessment in the proposed indication is positive for a population of patients which currently do not have other approved treatment options.

*Complications of allogeneic HSCT:* The sponsor considers that current data does not indicate an identified safety risk regarding an increase in transplant related mortality or increased severity of GVHD when allogeneic HSCT is performed following nivolumab therapy.

However, in response to the TGA request, the sponsor agrees to add '*Complications of allogeneic HSCT following nivolumab therapy*' as an Important Potential Risk to the RMP and ASA. Consequently, the sponsor has also added the same text from the EU SmPC on this potential risk into the proposed Australian PI. Lastly, information on this safety concern will also be added to the irAR Management Guide which is the Australian HCP risk management tool for nivolumab.

The sponsor plans to initiate a registry study (Study CA209835) in 2017 which will prospectively collect data on post- allogeneic HSCT complications in patients who were previously exposed to nivolumab and receive subsequent allogeneic HSCT. Information from this study will be used to update the EU-RMP/ASA appropriately.

*Safety in the elderly:* The sponsor does not believe that any changes to the PI are warranted regarding the use of nivolumab in elderly patients and that the current wording which is aligned to that of the EU SmPC and US PI is sufficient. Although there was a numerical increase in SAEs in patients aged > 65 years. This would be in keeping with an expected greater preponderance for hospitalisation in elderly patients, where hospitalisation/prolonged existing hospitalisation is the predominant reason for defining an AE as serious. There has been no causality association established between nivolumab use and the severity of AEs or number of DRAEs with age. All data generated in elderly patients has been descriptive in nature. The sponsor agrees that it is good clinical practice to monitor elderly patients closely for AEs and the nivolumab PI recommends this as a precaution for all patients.

*Risk minimisation documents:* The sponsor agrees to prominently display the internet address for the full PI on the HCP side of the PAC. In addition, the sponsor will prominently display the internet address for the full CMI on the patient side of the PAC.

The internet address for the full PI is already present on the back page of the irAR Management Guide, however the sponsor agrees to prominently display the internet address for the full PI on the front page of the irAR Management Guide.

The Pack Leaflet (pack insert) contains relevant information required by those HCPs (hospital pharmacists and infusion nurses) that are responsible for dispensing, preparing and administering nivolumab intravenous infusions. The prescribing healthcare professionals (medical oncologists) already have access to the full PI via multiple sources

including the TGA website, the sponsor's website or medicines.org.au. For the reasons stated, the sponsor does not feel it is necessary to include the internet address for the full PI within the pack insert.

*Risk management plan (RMP):* The sponsor can confirm that in parallel to this pre-ACM response, a response to the new and outstanding RMP recommendations will also be submitted along with an updated ASA (version 8.0) and an updated EU-RMP (version 6.2). As described above, the sponsor can confirm that the potential risk of 'Complications of allogeneic HSCT following nivolumab therapy' has been added to ASA version 8.

### **Conclusion**

The clinical data presented in this application demonstrates that nivolumab monotherapy (3 mg/kg Q2W) offers meaningful clinical benefit in heavily pre-treated cHL patients after failure of ASCT and brentuximab vedotin treatment. In addition, the overall safety profile of nivolumab monotherapy was consistent with the known and well characterised safety profile of the drug and was comparable to the profiles observed across other tumour types in terms of the type, frequency, and severity of AEs observed.

Based on the clinical data submitted with this application, the benefit/risk profile is favourable with a safety profile that is consistent with the current use of nivolumab monotherapy in the treatment of other malignancies. Approval of nivolumab for the treatment of Australian patients with cHL who fail ASCT and brentuximab vedotin will provide a new therapeutic alternative in a clinical setting where no treatment options currently exist and prognosis for survival is exceedingly poor.

### **Advisory Committee considerations**

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Opdivo concentrate solution for IV infusion vial containing 40 mg in 4 mL (10mg/mL) and 100 mg in 10 mL (10mg/mL) of nivolumab are of the opinion that there is an overall positive benefit-risk profile for the Delegate's amended 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.*

In making this recommendation the ACM

- Noted trial data was in adult patients (> 18 years old)
- Considered possible benefits to having separate safety data specific for Hodgkin lymphoma in the PI and CMI

### **Proposed conditions of registration**

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA,
- Negotiation of the Product Information and Consumer Medicine Information to the satisfaction of the TGA.

## **Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments**

The ACM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

### **Specific Advice**

The ACM advised the following in response to the delegate's specific questions on the submission:

1. *Are there any implications from the PK modelling for clinical usage and precautions? Is this aspect of the proposed PI adequate?*

ACM advised that the proposed PK modelling for clinical usage and precautions has minimal implications. ACM noted small numbers in these studies and that this medication is already used in a wide variety of patients.

The ACM advised that the proposed PI is adequate noting the observed PK differences and relevant influential covariates (based on available data and analysis) are adequately described in the PI. The ACM also noted that the pharmacokinetics in patients with classical Hodgkin lymphoma (cHL) are not be optimally characterized, but have been replicated in subsequent PK modelling analysis. The ACM further noted that the higher exposure in people with cHL may have implications for dosing.

2. *Efficacy: What are the views of the committee on the adequacy of the submitted interim study reports from Phase 1 and 2 trials and updated data as support for registration for the cHL indication. Is the notation about limitation of data adequate? Should the indication wording specify adult patients?*

ACM advised that the submitted interim study reports from Phase I and II trials and updated data as support for registration for the cHL indication demonstrates benefit from nivolumab in this small population of patients. ACM noted that this is an area of unmet need, and in accordance with other jurisdictions, is reasonable to recommend approval. ACM also noted that the notation about data limitation is needed and is clear.

3. *Safety: Is the available information sufficient for the anticipated clinical setting? Is the proposed PI/CMI with pooled safety data across all indications, and other clinical information, adequate in this regard?*

ACM advised that the available information is sufficient for the anticipated clinical setting. ACM noted a concern regarding subsequent allogeneic transplantation, however the numbers of patients in this group are small and that the wording in the PI needs to be decided on a case by case basis. ACM also noted that the relevant statistics are addressed in the PI as well.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

### **Outcome**

Based on a review of quality, safety and efficacy, the TGA approved the registration of Opdivo concentrate solution for intravenous infusion vial containing nivolumab 40 mg in 4 mL and 100 mg in 10mL indicated for:

*'Opdivo, as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell*

*transplant and treatment with brentuximab vedotin. The approval of this indication is based on objective response rate. See Clinical Trials.'*

The full indications are now:

*'Opdivo, as monotherapy is indicated for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma.*

*Opdivo, in combination with YERVOY (ipilimumab) is indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH).*

*Opdivo, as monotherapy is indicated for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy.*

*Opdivo, as monotherapy is indicated 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.*

*Opdivo as monotherapy is indicated for the treatment of patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy in adults.*

*Opdivo, as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant and treatment with brentuximab vedotin. The approval of this indication is based on objective response rate. See Clinical Trials.'*

### **Specific conditions of registration applying to these goods**

- The Opdivo EU-RMP (version 6.2, dated 27 January 2017, data lock point 26 May 2016), with Australian Specific Annex (version 8.0, dated 17 March 2017), submitted with this application, and any future updates, must be implemented.
- The final CSR documents for Studies CA209205 and CA209039, including completed analyses, should be provided to the TGA when available.

## **Attachment 1. Product Information**

The PI for Opdivo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## **Attachment 2. Extract from the Clinical Evaluation Report**



## **Therapeutic Goods Administration**

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