Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Nivolumab

Proprietary Product Name: Opdivo

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

21 February 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About the Extract from the Clinical Evaluation Report

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

Contents

List of common abbreviations

Abbreviation	Meaning
ADA	Anti-drug antibody
AJCC	American Joint Committee on Cancer
AM	'adjuvant melanoma'
BW	Body weight
CO	Clinical overview
CSR	Clinical study report
DMC	Data Monitoring Committee
DMFS	Distant metastasis-free survival
HR	Hazard ratio
IMAE	Immune-mediated Adverse events
IrAEs	Immune-related Adverse events
IRC	Independent review committee
ITT	Intention to treat
NAB/NAb	Neutralizing anti-drug antibody
NED	No evidence of disease
OESI	Other event of special interest
OS	Overall survival
Pop PK	Population pharmacokinetics
PP	Per protocol
PS	Performance status
RFS	Recurrence-free survival
q	every (for example, q 2 weeks=every 2 weeks)
Q2W	Every 2 weeks
SCS	Summary of clinical safety

Abbreviation	Meaning
SJS	Stevens-Johnson Syndrome
TEN	Toxic epidermal necrolysis
VPC	Visual predictive check

1. Submission details

1.1. Identifying information

Submission number	PM-2017-03752-1-4
Sponsor	Bristol-Myers Squibb
Trade name	Opdivo
Active substance	Nivolumab

1.2. Submission type

This is a Category 1 application for approval of Extension of Indications for nivolumab to include use as an adjuvant treatment for patients with completely resected Stage III or Stage IV melanoma. It was designated as a Priority review.

1.3. Drug class and therapeutic indication

Nivolumab is a fully humanised monoclonal antibody antineoplastic agent, a PD-1 blocking antibody with WHO ATC code L01XC17.

Current indications approved in Australia are:

> *'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.*
>
> *Opdivo as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum based therapy.'*
>
> *Opdivo, as monotherapy is indicated for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy.*

The approval of this indication is based on objective response rate and duration of response in a single arm study.'

Proposed extension of indications

The letter of application states that the Australian proposed new indication is as follows:

'Opdivo as monotherapy is indicated for the adjuvant treatment of patients with completely resected Stage III or Stage IV melanoma.'

1.4. Dosage forms and strengths

Nivolumab is presented as a concentrated solution for infusion, 10 mg/mL.

Registered product strengths are in 10 mL vials; 40 mg/4mL AUSTR 231867 and 100 mg/10 mL AUSTR 231868.

2. Background

2.1. Information on the condition being treated

The sponsor's letter of application notes that Australia has one of the highest incidence rates of newly diagnosed cases of malignant melanoma in the world. In 2017, it is estimated that the age–standardised incidence rate will be 50 cases per 100,000 persons (62 for males and 39 for females). It is the fourth most commonly diagnosed cancer in Australia and approximately 14,000 diagnoses are expected in 2017, with estimated 1800 deaths. While incidence rates increase with age, and is highest in men over 65 years, a substantial group are in the age range 25-49 years, with estimated 2500 likely to be diagnosed in this age group in 2017.

The incidence in Australia and New Zealand mentioned in the clinical overview of the dossier was about 40/100,000 compared to 20/100,000 in the USA, and approximately 10 per 100,000 for UK, France and Germany (references to data are from 2007-2011). The RMP–Australian Specific Annex provided with the submission states that the age-standardised incidence rate in 2013 was 50.3 cases per 100,000 and mortality rate (age standardised) in 2014 was 5.5 deaths per 100,000.

In Australia between 2009 and 2013, individuals diagnosed with melanoma skin cancer overall had a 90% chance (88% for males and 93% for females) of surviving for 5 years compared to their counterparts in the general Australian population. Between 1984–1988 and 2009–2013, the 5 year relative survival from melanoma skin cancer improved from 86% to 90%.[1]

Treatment for cutaneous malignant melanoma includes surgical removal of the primary growth and surrounding normal tissue and sentinel lymph node biopsy to determine stage.

Despite surgical treatment, melanoma patients with Stage III disease that has spread to regional lymph nodes are at high risk for recurrence and death. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand 2008 refer to adjuvant treatment at Section 14, on page 93, stating that patients with pathologic Stage IIC and IIIB/C are at high risk of dying of melanoma (< 50% 10 year survival) and should be considered for adjuvant therapy, although the recommendations included observation as acceptable management.[2]

[1]AIHW 2017 Cancer compendium https://www.aihw.gov.au/reports/cancer/cancer-compendium-information-and-trends-by-cancer-type/report-contents/melanoma-skin-cancer-in-australia

[2] Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand 2008; Cancer Council Australia/Australian Cancer Network/Ministry of Health, New Zealand (2008).

Overall 5 year recurrence rates for Stage IIIA, IIIB, and IIIC patients are stated by the sponsor to be 37%, 68%, and 89%, respectively, with the site of first recurrence being local/in-transit (28%), regional nodal (21%), or systemic (51%).[3] These frequencies were derived from retrospective analysis of 340 patients with AJCC (2002) Stage III melanoma, followed-up by the institution by a standard approach, after being rendered free of disease. Elsewhere the authors state '*We analyzed our entire database from this time period and found the overall 5 year risk of relapse at any site was 48% for Stage IIIA, 71% for Stage IIIB, and 85% for Stage IIIC patients'.* The intention of that study was to consider the rationale for the frequency and duration of follow-up; the data suggested a low probability of detecting first relapses by physical examination after 3 years for IIIA, 2 years IIIB, and 1 year for IIIC. There was a corresponding low probability of detection by CT scan beyond 3 years in IIA/B and 2 years in IIIC patients.

The Australian Cancer Treatments site eviQ lists interferon alfa-2b (rbe) (Intron A) as the only adjuvant treatment for malignant melanoma.[4] In contrast, ten treatment protocols reflect the risk-benefit of treatment for unresectable or advanced metastatic melanoma.

2.2. Current treatment options

As mentioned above, clinical guideline recommendations included observation as acceptable management for patients with resected Stage I-III melanoma.[5]

2.2.1. Intron A

In Australia the only registered product with an approved indication for adjuvant therapy in melanoma is interferon alfa 2b (Intron A). Intron A was first registered in 1999. Intron A is approved for two hepatitis indications, and for six oncology indications that include the following:

> *'Malignant Melanoma: Intron A is indicated as an adjuvant therapy of malignant melanoma following surgery in patients who are at high risk of recurrence. The potential benefit to the patient should be assessed carefully. Although toxicity of the treatment may be substantial, for most patients, the benefit of therapy outweighed the risk.'*[6]

The dosage registered for malignant melanoma is 20 million IU /m^2 daily for 5 days/week intravenously over a 4 week period for induction and 10 million IU/m^2 daily 3x per week subcutaneously as maintenance. This is consistent with the 'high dose' interferon in the 2008 Australian/NZ clinical practice guideline.[2]

This Australian/NZ Clinical Practice Guideline for the Management of Melanoma in Australia and New Zealand states:

> *'Multiple trials have shown that high-dose interferon improves relapse-free survival by approximately 10% at five years, but initially reported benefits in overall survival have disappeared with longer follow-up periods. An individual patient data meta-analysis of ten of 13 observation-controlled trials of various dosing regimens showed a statistically significant benefit of interferon for event-free survival, and an absolute overall survival benefit of 3% (CI 1%–5%) at five years. In this meta-analysis there was no evidence of*

[3]Diagnosis and treatment of melanoma European consensus-based interdisciplinary Guideline –Update 2016 European journal of cancer 63(2016) 201-217 http://www.sciencedirect.com/science/article/pii/S0959804916321360?via%3Dihub and https://ac.els-cdn.com/S0959804916321360/1-s2.0-S0959804916321360-main.pdf?_tid=5e289234-c5db-11e7-88ae-00000aacb361&acdnat=1510293343_6c5821d982250fbdb3617dea4fa831cf

[4] See eviQ medical oncology/melanoma https://www.eviq.org.au/medical-oncology/melanoma

[5] Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand 2008; Cancer Council Australia/Australian Cancer Network/Ministry of Health, New Zealand (2008).

[6] Intron A Australian PI https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-05778-3&d=20171115161146224 83

difference according to dose or duration of therapy. Individual Phase III trials of intermediate and low-dose have not shown a clear advantage for interferon over observation'.

The guideline noted that the toxicity of high-dose interferon-alpha is substantial but reversible, and requires experienced medical oncology management, aggressive supportive measures including the use of prophylactic antidepressants, with careful monitoring and dose-reduction strategies, particularly for hepatotoxicity. Because of the toxicity of high-dose interferon, and the uncertain and modest benefits of lower-dosing regimens, clinical trials of new adjuvant therapies were strongly encouraged; observation was considered an appropriate comparator in Phase III trials.

Products registered elsewhere include pegylated interferon therapy. Clinical Guidelines state 'Long-term pegylated interferon improved four-year relapse-free survival by 7% but had no effect on distant metastasis-free survival or overall survival.[2] There was a high discontinuation rate due to high-grade toxicities including fatigue, hepatotoxicity and depression.

2.2.2. Ipilimumab

In the USA ipilimumab 10 mg/kg is approved as adjuvant treatment of fully resected Stage III melanoma.

Table 1: Registration studies for adjuvant treatment

Population	Investigational treatment	Comparator	Outcome
Study ECOG E1684; Randomised Adjuvant to surgical treatment in patients with melanoma who were free of disease (post-surgery) but at high risk for systemic recurrence. These included patients with lesions of Breslow thickness >4 mm, or patients with lesions of any Breslow thickness with primary or recurrent nodal involvement.	Intron A therapy: 20 million IU/m2 intravenously five times per week for 4 weeks (induction phase) followed by 10 million IU/m2 subcutaneously three times per week for 48 weeks (maintenance phase). Intron A therapy was begun ≤56 days after surgical resection. N = 143 patients	Observation: N = 137	K-M estimated 5 year relapse-free survival rate Intron A 37% versus observation 26%. Median time to relapse Intron A 1.72 years versus observation patients 0.98 years (p=0.01, stratified Log Rank). K-M estimated 5 year OS rate 46% for Intron A treated patients versus 37% for observation patients. Median overall survival time for Intron A 3.82 years versus 2.78 years (p=0.047, stratified Log Rank). Initially approved Australia 1997; has Indication for adjuvant therapy of malignant melanoma following surgery in patients who are at high risk of recurrence.

Population	Investigational treatment	Comparator	Outcome
Study CA184029 (EORTC 18071) Phase III, randomised; after complete resection of high-risk Stage III melanoma, Overall, 20%/44%/36% of subjects had Stage IIIa/IIIb/IIIc disease, 42% had ulcerated primary tumours, and 58% had macroscopic lymph node involvement.	Adjuvant immunotherapy with ipilimumab 10 mg/kg N=475	Placebo: N = 476	The 5 year RFS (reported 2016) was ipilimumab 40.8% versus placebo 30.3%, HR recurrence (95% CI) 0.76 (0.64, 0.89, P < 0.001). Median follow-up 5.3 years; median RFS ipilimumab 27.6 months versus placebo 17.1 months. OS rate 5 years 65.4% ipilimumab group versus 54.4% placebo group (hazard ratio for death, 0.72; 95.1% CI, 0.58 to 0.88; P = 0.001) Approved FDA 2015 for adjuvant treatment of resected cutaneous melanoma with regional nodes. **Comment** Ipilimumab is not approved in Australia for this Indication.

The relevant US FDA approval letter for ipilimumab is '*for a new indication for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm, who have undergone complete resection including total lymphadenectomy*'[7]

The current FDA-approved label for ipilimumab is available at the accessdata.fda.gov website.

2.2.3. Nivolumab

In the USA, FDA approved an additional indication corresponding to this submission, for the treatment of resected melanoma in the adjuvant setting, on 20 December 2017.[8]

Comment: The risk of toxicity of Intron A compared to benefit has apparently resulted in limited use for adjuvant treatment of melanoma following surgery. Nevertheless it is a registered product in Australia with indications that include adjuvant therapy in malignant melanoma following surgery in patients who are at high risk of recurrence.

See Section 7.3 and 7.4 for consideration of Study CA184029, regarding the use of ipilimumab as the comparator in the pivotal trial for nivolumab.

2.3. Clinical rationale

The sponsor provided the reasoning as summarised below for the use of nivolumab as adjuvant therapy in resected Stage IIIB/C and Stage IV melanoma:

- Post-resection, most patients with Stage III and IV disease will develop unresectable recurrences. Unresectable disease has high mortality even with new treatments for advanced melanoma. There is a rising incidence. Younger age groups lose productive years.

[7] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125377Orig1s073ltr.pdf
[8] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125554s055lbl.pdf

- Current treatments do not show clear clinical benefit and have substantial toxicity.
- Ipilimumab is not approved for adjuvant melanoma treatment in Australia; it is approved in the USA for Stage III patients after complete resection.

The sponsor concluded there is unmet clinical need in Australia for adjuvant treatment for this patient population. Nivolumab is approved in Australia as monotherapy for treatment of advanced (unresectable Stage III or metastatic (Stage IV)) melanoma.

2.4. Formulation

No change to the registered formulation was proposed with this submission. No Quality data were provided and a Quality evaluation was not required for this submission.

2.5. Regulatory history

2.5.1. Australian regulatory history

Nivolumab was first registered in January 2016. Nivolumab Opdivo has since been approved for multiple oncology indications, including the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma, and in combination with Yervoy (ipilimumab), the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH).

2.5.2. Orphan/Priority designation

Orphan designation was not applicable to this submission.

The application for nivolumab for the proposed indication was accepted for Priority review designation.

2.5.3. Related submissions

Priority designation for the current submission

2.6. Guidance

- EMA/CHMP/205/95/Rev.4 Guideline on the evaluation of anticancer medicinal products in man
- It was noted there is a newly adopted guideline, effective from 1 April 2018 by the EMA, and not yet adopted by TGA; EMA/CHMP/205/95/Rev.5.

  Of note, this new guideline states, on Page 39/43, '*As there is often no way to identify the 'true' incidence of an ADR, the least biased measure should be consistently used. For events fulfilling the causality requirement of ADR, the frequency categories in the tabulated list of adverse reactions should therefore be based on the frequencies of all-causality AEs (that is, irrespective of investigators' assessments of relatedness).*'
- CPMP/EWP/2330/99: Points to consider on application with 1. Meta-analyses; 2. One pivotal study'.

2.7. Evaluator's commentary on the background information

The available background information is acceptable.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

- One interim pivotal CSR for Study CA209238, an ongoing Phase III randomised double-blind efficacy and safety trial of nivolumab (n = 452) versus ipilimumab (n = 453) in subjects with completely resected Stage IIIB/C or Stage IV 'NED' melanoma who are at high risk for recurrence.
- One supporting CSR with two addenda for CA184029, an ongoing Phase III randomised double-blind efficacy and safety trial of ipilimumab (n= 471) versus placebo (n = 474) in subjects with complete resection of Stage IIIA, IIIB and IIIC cutaneous melanoma.
- Population PK study report 930118022 v1.0 nivolumab PopPK analysis of adjuvant treatment nivolumab monotherapy in resected Stage IIIB/C or Stage IV melanoma.

3.2. Paediatric data

No paediatric data were provided.

Although the pivotal trial protocol allowed for the enrolment of patients 15 -18 years in countries where this was permitted, no subjects < 18 years of age were enrolled.

The application form states the sponsor is not seeking approval for paediatric use in this application. The letter of Application also confirms the Australian proposed indication, which does not refer to age of patients.

3.3. Good clinical practice

According to each CSR, the studies were conducted in accordance with GCP and protected the rights of subjects. The protocol amendments and subject informed consent forms received appropriate approval prior to initiation of study at the site.

An independent Data Monitoring Committee (DMC) was utilised to provide oversight of safety and efficacy considerations in Study CA209238, and to provide advice to the sponsor for the continuing protection of subjects enrolled in the trial. The DMC acted in an advisory capacity, and monitored subject safety and evaluated the available efficacy data for the study.

Efficacy was reviewed by the DMC as part of the benefit-to-risk assessment. The DMC reviewed the formal interim analysis results for RFS.

3.4. Evaluator's commentary on the clinical dossier

The clinical dossier was clearly set out with the relevance of each section adequately described in the letter of application.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

The summary of clinical pharmacology for the adjuvant melanoma study refers to previous studies. The pharmacokinetics (PK) of nivolumab in solid tumours and cHL has been characterised by Pop PK analysis. There were no new specific PK studies provided with this

submission for healthy subjects or the target population. There were no new PK studies for special populations or drug-drug interactions provided with the submission for this application.

The Pop PK analysis report provided with this submission notes that PK, clinical activity, and safety of nivolumab have been assessed in several Phase I, Phase II, and Phase III clinical studies in adult subjects with solid tumours, including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), advanced melanoma, renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), and gastric cancer (GC), and in the haematologic tumour, classical Hodgkin's lymphoma (cHL). Nivolumab 3 mg/kg given once every 2 weeks (Q2W) was the dose for these indications where approved.

The PopPK analysis described in this report was intended to characterise the PK of nivolumab in adjuvant melanoma subjects combined with PK from prior studies in different tumour types.

Analysis evaluated the PK in adjuvant melanoma relative to metastatic/advanced melanoma and the historical reference tumour type, second line use in non-small cell lung cancer (NSCLC 2L+).

Table 2: Newly submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
Population PK analyses	Healthy subjects	n/a	
	Target population	PopPK analysis CA 209238	
	Other	See previous evaluations	

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Table 3: Pharmacokinetic results excluded from consideration

Study ID	Subtopics	PK results excluded	Synopsis
N/A			

4.2. Summary of pharmacokinetics

The following summary is derived from the current Australian nivolumab 'Opdivo' PI.[9]

4.2.1. Physicochemical characteristics of the active substance

CAS: 946414-94-4. Opdivo (nivolumab (rch)) is a fully human anti-PD-1 monoclonal antibody (IgG4) produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology. The product is a clear to opalescent, colourless to pale yellow liquid for intravenous infusion that may contain few light particles. Each 1 mL contains 10 mg nivolumab and 2.50 mg sodium. The solution has a pH of approximately 6.0 and osmolality is approximately 340 mOsm/kg.

[9] https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2016-PI-01052-1&d=20171117161146224 83

4.2.2. Pharmacokinetics in healthy subjects

Not applicable: PK was assessed using a population PK approach using data from oncology patients.

4.2.3. Pharmacokinetics in the target population

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_{avgss}). The lower nivolumab clearance was not considered clinically meaningful; there was a flat predicted exposure-response relationship.

Nivolumab CL increased with increasing body weight. Body weight normalised dosing produced approximately uniform steady-state trough concentration over a wide range of body weights (34-162 kg).

The metabolic pathway of nivolumab has not been characterised. As a fully human IgG4 monoclonal antibody, nivolumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. (PI v9.0 page3)

4.2.4. Pharmacokinetics in special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with mild hepatic impairment (total bilirubin 1.0 × to 1.5 × ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n = 92) compared to patients with normal hepatic function (total bilirubin and AST ≤ ULN; n = 804) in the population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild hepatic impairment and normal hepatic function. Nivolumab has not been studied in patients with moderate (total bilirubin > 1.5 × to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3 × ULN and any AST). PI v 9.0 page3

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

The effect of renal impairment on the CL of nivolumab was evaluated in patients with mild (GFR < 90 and ≥ 60 mL/min/1.73 m2; n = 379), moderate (GFR < 60 and ≥ 30 mL/min/1.73 m2; n = 179), or severe (GFR < 30 and ≥ 15 mL/min/1.73 m2; n = 2) renal impairment compared to patients with normal renal function (GFR ≥ 90 mL/min/1.73 m2; n = 342) in population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate renal impairment and patients with normal renal function. There were insufficient data to determine the effect of severe renal impairment on the CL of nivolumab. PI v9.0 pages 3-4

4.2.4.3. Pharmacokinetics in relation to other population characteristics

Population PK analysis suggested no difference in CL of nivolumab based on age, gender, race, solid tumour type, tumour size, and hepatic impairment. The majority of patients in this analysis were diagnosed with NSCLC. Although ECOG status, baseline glomerular filtration rate (GFR),

body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful.

Patients with lower baseline serum albumin tended to have lower exposure to nivolumab. However, because of the flat exposure-response relationship between nivolumab exposure and overall survival, this effect is unlikely to be clinically meaningful and no dose adjustment is recommended for patients with lower serum albumin. PI v9.0

4.2.5. Population pharmacokinetics

As noted above, PK information was derived from previous population PK analyses in patients with a range of tumours.

4.2.5.1. Population PK analysis in Study CA 209238

The report describes the results of Pop PK analysis of adjuvant treatment with nivolumab monotherapy for '*Stage IIIb/c or Stage IV melanoma in subjects who have undergone complete resection and are at high risk of recurrence*'. The objectives were to characterise population PK of nivolumab in adjuvant melanoma subjects relative to advanced melanoma subjects, and compare summary measures of nivolumab exposure produced by a nivolumab dose of 240 mg every 2 weeks relative to those produced by 3 mg/kg Q2W in the adjuvant melanoma population.

Analysis was performed using data from all subjects enrolled in studies listed, where nivolumab concentrations were available; Phase I studies were also included. A total of 1773 subjects were included in the dataset, with a total of 11,644 samples. PK variables, demographic and physical characteristics, baseline disease characteristics and eGFR were included in the analysis dataset.

It was hypothesised that clearance (CL) may not change with time in adjuvant melanoma subjects, since the median estimate of adjuvant melanoma baseline CL was estimated to be lower than the steady state CL for the other tumour types

The final model included:

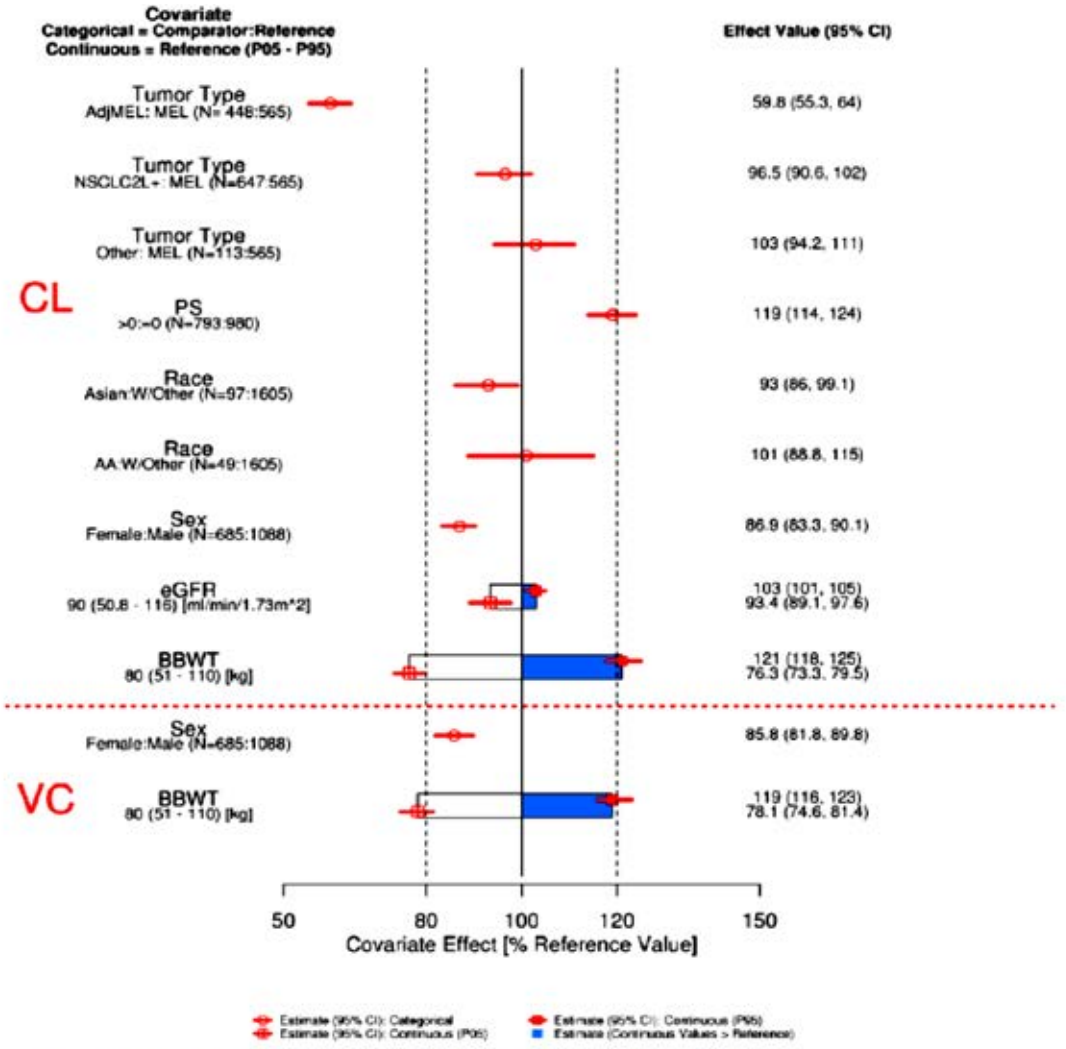
- Stationary CL on adjuvant melanoma and time-varying CL on all other tumour types.
- The effect of adjuvant melanoma on baseline CL.

This model was a two-compartment, zero-order IV infusion with stationary CL for adjuvant melanoma and time-varying CL (sigmoidal-Emax function) for advanced melanoma, NCSLCL2L+ and the other tumour types.

The magnitude of the effect of PS, BW and eGFR on CL, and the effect of sex and BW on volume of central compartment (VC) for the current model, that includes adjuvant melanoma, was comparable to that previously reported in subjects with other tumour types including advanced melanoma, NSCLC, SCLC, UC, GC, RCC, and SCCHN.

The model predicted that the baseline CL in subjects with adjuvant melanoma was 40% lower relative to CL in advanced melanoma subjects; the figure below is copied from page 46 of the PPK report.

Figure 1: Covariate effect on Pop PK model parameters (Final model)



Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.
Note 3: Reference subject is white/others male age=65 yr, PS=0, eGFR=90 ml/min/1.73m^2 and body weight=80kg, subject with normal hepatic function with advanced melanoma. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value. AA under race indicates African American.
Confidence Interval values are taken from bootstrap calculations (500 successful out of a total of 500)
Analysis -Directory: /global/pkms/data/CA/209/238/prd/ppk/final/
R-Program Source: Analysis-Directory/R/scripts/ cov-eff-plot-FinalModel.r'
Source: Analysis-Directory/R/plots/a-model3-cov-eff-plot.png

Adjuvant melanoma subjects have a 13-45% higher predicted dose-normalised exposure relative to the advanced melanoma subjects after the first dose and at steady state; see copy below of Table 5.1.3.1-3 from the Pop PK report (Table 4).

Table 4: Summary statistics of individual measures of dose normalised nivolumab exposure for subjects with adjuvant melanoma and advanced melanoma Q2W

Parameter	Adjuvant Melanoma (N=448)	Advanced Melanoma (n=530)	
	Geometric Mean (%CV)	Geometric Mean (%CV)	% Diff[a] (%)
Dose-Normalized C_{min1} [(μg/mL)/(mg/kg)]	8.24(19.7)	5.87(27.0)	40.4
Dose-Normalized C_{max1} [(μg/mL)/(mg/kg)]	22.4(135)	19.7(50.4)	13.7
Dose-Normalized C_{avg1} [(μg/mL)/(mg/kg)]	11.5(20.5)	9.31(22.4)	23.5
Dose-Normalized C_{min2} [(μg/mL)/(mg/kg)]	31.9(30.3)	22(64.3)	45.0
Dose-Normalized C_{max2} [(μg/mL)/(mg/kg)]	55.5(62.3)	42.9(44.6)	29.4
Dose-Normalized C_{avg2} [(μg/mL)/(mg/kg)]	39.2(26.4)	28.8(52.6)	36.1

[a] Calculated as $(Geo.Mean_{AdjMEL} - Geo.Mean_{AdvMEL})/Geo.Mean_{AdvMEL}*100$

The geometric mean estimates of nivolumab exposures for Japanese subjects with adjuvant melanoma are approximately 20% lower than non-Japanese subjects. While the point estimates are trending lower for Japanese subjects, the concentration distribution is within the concentration distribution of the non-Japanese subjects.

The distribution of nivolumab exposures across the body weight ranges of subjects from Study CA209238 (median 80 kg, range 39 to 183 kg) were below the median and the 95th percentile for the exposures from nivolumab 10 mg/kg Q2W dosing regimen in which safety was previously established.

The Pop PK model was considered to provide an adequate description of nivolumab concentration-time data in the target population.

Of note, the analyses showed that adjuvant melanoma subjects start treatment with a CL that is approaching the steady state CL predicted post-treatment for advanced melanoma subjects, as these subjects are relatively healthier than advanced melanoma subjects. In Study CA209238, the performance status of the subjects at baseline was 0 for 91% of the subjects as compared to 64% in advanced melanoma subjects.

4.2.6. Pharmacokinetic interactions

Pharmacokinetic interaction studies have not been conducted. Nivolumab is a human monoclonal antibody. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolizing enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of nivolumab. Nivolumab is not expected to have an effect on CYP or other drug metabolizing enzymes in terms of inhibition or induction. PI v9.0 page 39

4.3. Evaluator's overall conclusions on pharmacokinetics

Previous nivolumab Pop PK analyses were acceptable. From a regulatory perspective, the analysis attached to this submission would also be acceptable.

Adjuvant melanoma subjects have a 13-45% higher predicted dose-normalised exposure relative to the advanced melanoma subjects after the first dose and at steady state, due to differences observed in clearance between advanced and adjuvant melanoma patient populations. The evaluator has reservations about possible implications for optimal dosing with respect to safety if flat dosing is adopted.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

There were no specific PD studies provided with this submission.

5.2. Summary of pharmacodynamics

See current approved PI. Information from the PI has been included in the sections below for reference.

5.2.1. Mechanism of action

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb) which binds to programmed death-1 (PD-1) receptor and blocks its interaction with the ligands PD-L1 and PD-L2.

The PD-1 receptor is a negative regulator of T-cell activity. Engagement of PD-1 with PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth. Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumour responses in metastatic melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity.

5.2.2.2. Secondary pharmacodynamic effects

Cardiac Electrophysiology

The potential effect of nivolumab on QTc interval was evaluated in 146 patients at doses up to 10 mg/kg every three weeks. No changes in mean QT interval were detected in nivolumab-treated patients based on Fridericia correction method.

Ipilimumab did not have a clinically meaningful effect on the QTc interval at doses up to 10mg/kg. Thus, QT interval prolongation is not expected with the nivolumab and ipilimumab combination.

Immunogenicity

As with all therapeutic proteins, there is a potential for an immunogenic response to nivolumab.

Nivolumab Monotherapy:

In a pooled analysis of 1734 patients who were treated with nivolumab 3 mg/kg every 2 weeks and evaluable for the presence of anti-product-antibodies, 170 patients (9.8%) tested positive for treatment-emergent anti-product-antibodies by an electrochemiluminescent (ECL) assay. Only 2 (0.1%) patients were persistent positive. Neutralising antibodies were detected in only 10 (0.6% of the total) of the positive anti-product-antibody patients. There was no evidence of altered pharmacokinetic profile, or toxicity profile associated with anti-product-antibody development. Neutralising antibodies were not associated with loss of efficacy.

5.2.3. Time course of pharmacodynamic effects

No new information was provided.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

Exposure-response relationships were not discussed in the interim CSR for Study CA209238, or Pop PK analysis.

The sponsor's Summary of Clinical Pharmacology states these were not conducted because data were available from only one nivolumab dose level. However it is also noted that '*experience from the nivolumab E-R analysis of efficacy in RCC found that the results may be misleading if the effect of CL is not taken into account. In the initial E-R analysis of OS conducted in subjects with RCC (including data from a single phase 3 study which investigated a single dose level of nivolumab 3 mg/kg only), nivolumab exposure was found to be a significant predictor of OS. This was because the data from a single dose level was insufficient to resolve the potential confounding effect of CL on Cavgss. However, when data from subjects with RCC treated with additional dose levels were added to the RCC analysis, the confounding effect of CL on Cavgss was resolved, and nivolumab exposure was not a predictor for OS.*'

Furthermore '*E-R analysis of safety (Grade 3+ drug related adverse events [DR-AEs] and adverse events leading to discontinuation or death [AE-DC/D]) was previously performed in subjects with advanced melanoma, treatment refractory SQ and NSQ NSCLC, and advanced RCC subjects. In each of these analyses, the nivolumab exposure (Cavgss) produced by doses of 1 to 10 mg/kg did not appear to have a significant effect on the risk of Grade 3+ DR-AEs or AE-DC/D. Thus, an E-R analysis of safety was not conducted for adjuvant melanoma subjects from Study CA209238 as nivolumab 3 mg/kg Q2W has been shown to be safe and well-tolerated in multiple tumor types*.' Genetic, gender and age related differences in pharmacodynamic response

One objective of Study CA209238 was to evaluate PDL1 as a predictive biomarker for RFS. See Section 7.2.

ADAs and neutralising antibodies were assessed in the clinical study serum samples. See Section 8.5.

5.2.5. Pharmacodynamic interactions

No new information was provided.

5.3. Evaluator's overall conclusions on pharmacodynamics

See the analysis of Study CA209238 safety and efficacy, in particular with respect to PD-L1 status and anti-drug antibodies.

6. Dosage selection for the pivotal studies

No new information on dose-finding was provided. The single trial provided with this submission used the same weight-based dosing for adjuvant melanoma treatment as used for other tumour clinical trials, including advanced melanoma, that is, 3 mg/kg every two weeks.

This dose of nivolumab was selected for Study CA209238, based upon the totality of experience, as the dose expected to provide an appropriate balance of benefit and risk in Study CA209238.

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

The sponsor's Clinical Overview summarises of previous dose-finding studies in melanoma, in particular Study CA209003, a Phase I safety, efficacy and PK study with multidose escalation of doses 0.1, 0.3 , 1, 3, or 10 mg/kg every 2 weeks.

These doses were also used in combination with ipilimumab in Study CA209004.

Based upon the analyses of safety, efficacy, and Exposure-Response data from the Phase I Study CA209003, the dose 3 mg/kg was chosen.

6.2. Evaluator's conclusions on dose finding for the pivotal studies

The rationale for the dose utilised was acceptable for the clinical Trial CA209238.

7. Clinical efficacy

There was one Phase III efficacy and safety study of nivolumab used in the indication for adjuvant treatment of fully resected state IIIB/C and Stage IV melanoma.

Also provided was a CSR of the trial of the comparator ipilimumab against placebo.

7.1. Studies providing evaluable efficacy data

The available data for nivolumab in adjuvant melanoma is from the Phase III Study CA209238. The trial data provided for ipilimumab versus placebo were provided to justify the use of the active comparator, ipilimumab. The latter study also provided context for outcomes in a comparable patient group.

7.2. Pivotal or main efficacy studies

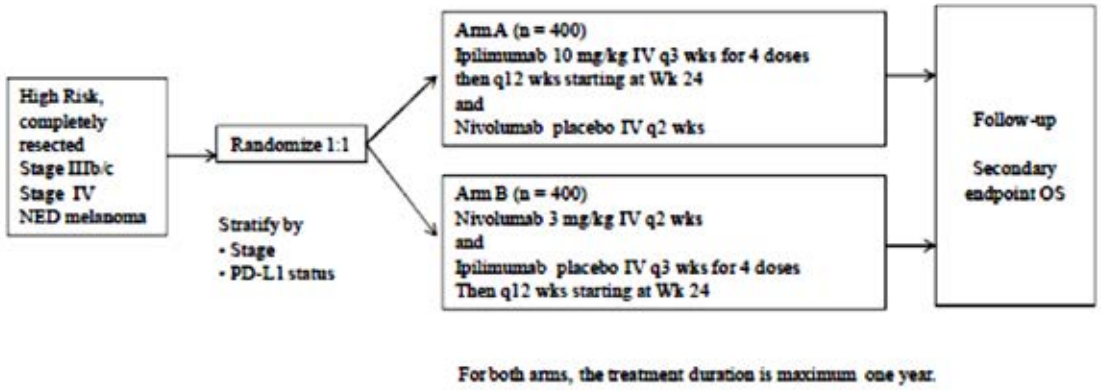
7.2.1. Study CA209238

7.2.1.1. Study design, objectives, locations and dates

Study CA209238 ('CheckMate 238: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 238') is a Phase III randomised, double-blind study of nivolumab versus ipilimumab in subjects with completely resected Stage IIIB/C or Stage IV melanoma.

Ipilimumab 10 mg/kg was chosen as the active comparator, based on superior recurrence-free survival (RFS) versus placebo (HR = 0.75 (95% CI 0.64, 0.90); p = 0.0013) and demonstration of a favourable benefit-risk profile as adjuvant treatment of resected Stage III melanoma in a randomised placebo-controlled Phase III study (Study CA184029/EORTC 18071).

Figure 2: Participant flow



The primary objective was to compare the efficacy, as measured by RFS, provided by nivolumab versus ipilimumab in subjects with completely resected Stage IIIB/C or Stage IV melanoma.

Secondary objectives included comparison of OS, safety and tolerability, PDL1 as predictive biomarker for RFS, and to evaluate the Health Related Quality of Life (HRQoL) as assessed by European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.

There were 130 sites in 25 countries. The enrolment period was from 16 March 2015 to 23 September 2015. The last patient last visit was 15 May 2017. The clinical study report (CSR) for Study CA209238 had a clinical database lock on 12 June 2017 (interim analyses including RFS, safety, immunogenicity, and PD-L1).

7.2.1.2. Inclusion and exclusion criteria

The intended study population was 'High risk', completely resected Stage IIIB/C and Stage IV melanoma subjects. Subjects enrolled had No Evidence of Disease ('NED') as described in the clinical trial protocol.

Key inclusion criteria:

- At least 15 years of age except: where local regulations and/or institutional policies do not allow for subjects < 18 years of age (paediatric population) to participate. For those sites, the eligible subject population is ≥ 18 years of age.
- All subjects must be either Stage IIIB/C or Stage IV AJCC (7th edition) and have histologically confirmed melanoma that is completely surgically resected in order to be eligible. Subjects must have been surgically rendered free of disease with negative margins on resected specimens. Appendix 1 includes the description of AJCC 7th editions of TNM and staging.

If Stage III melanoma (whether Stage IIIb or IIIc), the subjects usually have clinically detectable lymph nodes that are confirmed as malignant on the pathology report and/or ulcerated primary lesions. Subjects who are 'N2c' classification with 2-3 metastatic nodes and in transit metastases/satellites without metastatic nodes, or, 'N3'classification with any 'T' and 4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes are eligible. The pathology report for both Stage IIIb and IIIc must be reviewed, signed and dated by the investigator; this process will be confirmed during the IVRS randomisation call. *Clinically detectable lymph nodes* are defined as:

1. a palpable node (confirmed as malignant by pathology)
2. a non-palpable but enlarged lymph node by CT scan (at least 15 mm in short axis) and confirmed as malignant by pathology
3. a PET scan positive lymph node of any size confirmed by pathology

4. evidence of pathologically macrometastatic disease in one or more lymph nodes defined by one or more foci of melanoma at least 1cm in diameter

If Stage IV melanoma, the pathology report confirming negative margins must be reviewed, dated, and signed by the investigator prior to randomisation.

- Complete resection of Stage III disease that is documented on the surgical and pathology reports or complete resection of Stage IV disease with margins negative for disease that is documented on the pathology report.
- Complete resection must be performed within 12 weeks prior to randomisation
- All subjects must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomisation. Imaging studies must include a CT scan of the neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c or Stage IV disease, and brain magnetic resonance (MRI) or CT (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions).
- Tumour tissue from the resected site of disease must be provided for biomarker analyses. In order to be randomised, a subject must have a PD-L1 expression classification (positive, negative/or indeterminate) as determined by a central laboratory.

Subjects were to have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomisation. In addition, tumour tissue from the resected site of disease was required for biomarker analyses. In order to be randomised, a subject was required to have a PD-L1 expression classification (positive, negative, or indeterminate) as determined by the central laboratory.

Key exclusion criteria

- History of ocular/uveal melanoma
- Subjects with active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enrol.
- Subjects with previous non-melanoma malignancies are excluded unless a complete remission was achieved at least 3 years prior to study entry and no additional therapy is required or anticipated to be required during the study period (exceptions include but are not limited to, non-melanoma skin cancers; in situ bladder cancer, in situ gastric cancer, in situ colon cancers; in situ cervical cancers/dysplasia; or breast carcinoma in situ)
- Subjects with a condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids are permitted in the absence of active autoimmune disease.
- Prior therapy for melanoma except surgery for the melanoma lesion(s) and/or except for adjuvant radiation therapy (RT) after neurosurgical resection for central nervous system (CNS) lesions and except for prior adjuvant interferon (see qualifier below). Specifically subjects who received prior therapy with interferon, anti- PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways) are not eligible.
- Prior treatment with adjuvant interferon is allowed if completed ≥ 6 months prior to randomisation.

The last point means prior therapies for melanoma were exclusion criteria, *except* surgery for the melanoma lesion(s), and *except* adjuvant RT after neurosurgical resection for CNS lesions. Subjects who received prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways) were not eligible. However, prior treatment with adjuvant interferon *was* allowed if completed ≥ 6 months prior to randomisation.

The study protocol stated that 'eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.'

The CSR states that Source Data Verification (100%) of critical data was conducted for every first subject enrolled at a site and subsequently for 1 of every 10 subjects, so that 10% of subjects were source data verified for 100% of their critical data. With implementation of reduced source data verification (RSDV), source data verification was conducted for specific data points, such as the primary endpoint, death, AEs, events of special interest, and inclusion/exclusion criteria, as per the study-specific Site Monitoring Plan.

7.2.1.3. Study treatments

Ipilimumab group (N = 453): ipilimumab 10 mg/kg IV Q3W for 4 doses then Q12W starting at Week 24 (and nivolumab placebo IV Q2W)

Nivolumab group (N = 453): nivolumab 3 mg/kg IVQ2W (and ipilimumab placebo IV Q3W for 4 doses then Q12W starting at Week 24)

See Section 6; the nivolumab dose was selected as for other tumour indications.

The ipilimumab dose regimen of 10 mg/kg Q3W x 4 doses evaluated in this study was chosen based upon an analysis of data from 475 subjects randomised (471 treated) with ipilimumab 10 mg/kg Q3W in the Phase III Study EORTC 18071 (CA184029), which showed an RFS advantage of ipilimumab over placebo.

The dosing duration was capped at 1 year because 'very few subjects received ipilimumab beyond 1 year in the EORTC 18071 study. Despite the marketed approval of ipilimumab 3 mg/kg in the advanced melanoma setting, there was no data at the time of the start of Study CA209238 to support the efficacious use of ipilimumab 3 mg/kg in the adjuvant setting'.

Dose reductions and dose delays were not permitted; doses could be omitted based on criteria specified in the protocol.

7.2.1.4. Efficacy variables and outcomes

The primary efficacy variable was recurrence-free survival (RFS), as a surrogate for overall survival. The primary endpoint of RFS was stated in the SAP to be programmatically determined based on the disease recurrence date provided *by the investigator.*

RFS was defined as the time between the date of randomisation and the date of first recurrence (local, regional or distant metastasis, confirmed by pathology and/or imaging), new primary melanoma, or death (whatever the cause), whichever occurs first.

According to the protocol, *screening* efficacy assessment surveillance assessments were '*CT scan neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c and Stage IV and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions)*.' *CSR Protocol Appendix 1.1*

After complete resection of melanoma lesions, there is no measurable disease to follow. During the study, subjects were to be evaluated for the presence or continued lack of tumour. In addition to physical examination, the *on-treatment* assessments listed the same scans as at screening, using the same imaging method as used at screening/baseline, to be conducted every 12 weeks (±7 days) from first dose of study treatment through 12 months (until local, regional,

or distant recurrence (whichever comes first) for Stage IV subjects and until distant recurrence for Stage III subjects.

These tests would also occur every 12 weeks (±14 days) as follow-up to 24 months, then every 6 months through and up to year 5. If a subject starts systemic therapy for melanoma recurrence after study drug discontinuation, follow-up scans should be discontinued. If a subject starts systemic therapy for a new non-melanoma tumour after study drug discontinuation, follow-up scans can be done as per standard of care.

Recurrence is defined as the appearance of one or more new melanoma lesions, which can be local, regional, or distant in location from the primary resected site. Cytology and/or histology are mandatory to confirm recurrence in solitary /doubtful, cutaneous, subcutaneous or lymph node lesions. Tumour markers or auto-antibodies alone cannot be used to assess recurrence.

A subject who had disease at baseline was considered to have an event on the day of randomisation. A subject who died without reported recurrence was considered to have disease recurrence on the date of death.

For subjects who remained alive and whose disease had not recurred, RFS was censored on the date of last evaluable disease assessment.

For subjects who received subsequent anticancer therapy or who reported second non-melanoma primary cancer without prior recurrence reported, RFS was censored at the date of last evaluable disease assessment prior to or on the date of initiation of subsequent therapy or date of diagnosis of second non-melanoma primary cancer, respectively.

For those subjects who remained alive and had no recorded post-randomisation disease assessment, RFS was censored on the day of randomisation.

The censoring scheme is described below:

Table 5: Censoring scheme for primary definition of RFS

Situation	Date of Event or Censoring	Outcome
Recurrence (local, regional, distant, new primary melanoma)	Date of first recurrence	Event
Death without recurrence	Date of death	Event
Disease at baseline	Date of randomization	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No recurrence and no death	Date of last evaluable disease assessment	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without recurrence reported prior to or on the same day of disease assessment	Date of last evaluable disease assessment prior to or on the same date of initiation of subsequent therapy	Censored
Second non-melanoma primary cancer reported prior or on the same day of disease assessment	Date of last evaluable disease assessment prior to or on the same date of diagnosis of second non-melanoma primary cancer	Censored

Further details are given about handling of RFS events below.

The source of RFS event will be summarised as follows:

- Recurrence
  - Disease at baseline
  - Local recurrence
  - Regional recurrence (in-transit) metastatic or regional node recurrence)
  - Distant metastasis

- Death

The status of the subjects who are censored in the RFS KM analysis will be tabulated using following categories:

- Censored on randomisation date
  - No baseline disease assessment
  - No on study disease assessment and no recurrence/death
- Censored on date of last disease assessment on study
  - Received subsequent anti-cancer therapy
  - Second non-melanoma primary cancer
  - Still on treatment
  - In follow-up
  - Off study
    - Lost to follow-up
    - Subject withdrew consent
    - Other

New primary melanoma

The CSR states RFS is standard efficacy measure for adjuvant trials and was chosen because the intention of the trial was to ascertain whether 'prophylactic immunotherapy' after a complete resection prevents recurrence. It was considered that post-recurrence /progression therapy will be a confounder of overall survival.

> *RFS is frequently used as the efficacy measure for adjuvant trials and was chosen as the primary endpoint for Study CA209238 given the established correlation of RFS and OS with immunotherapy (ipilimumab) in adjuvant melanoma and the known safety profile of nivolumab, in line with the requirements of the EMA anticancer guidelines. RFS was also chosen because of the unmet medical need in Stage III patients with complete resection and the desire to treat the disease before it becomes metastatic. Additionally, OS was included as a secondary endpoint, but, with the availability of marketed agents that are known to improve OS, post-recurrence/ progression therapy may confound the assessment of OS.*
>
> *RFS benefit with nivolumab adjuvant treatment is expected to translate to an improvement in OS, as improvements in 5-yr RFS and OS rates were highly correlated at ~10% in CA184029 for ipilimumab versus placebo (40.8% versus 30.3% and 65.4% versus 54.4%, respectively). CO page 14*

Secondary efficacy endpoints included in this CSR were

- RFS endpoint by PD-L1; PDL-1 expression was defined as percent of tumour cells membrane staining in a minimum of 100 evaluable tumour cells per validated Dako PD-L1 IHC assay, referred to as 'quantifiable PD-L1 expression'. In this study PD-L1 'positive status' is defined as ≥ 5% tumour cell membrane staining within a tumour tissue sample. Exploratory analyses evaluated different thresholds for PD-L1 positivity at 1% and 10% tumour cell expression cut-off.
- QLQ-C30 responses to evaluate health-related quality of life.

Exploratory endpoints were:

- distant metastasis-free-survival (DMFS) for Stage III subjects

- association of BRAF mutation status with RFS and DMFS
- serum ADA/NAB to ipilimumab/nivolumab,
- EQ-5D responses and WPAI:GH work-related activity questionnaire

Overall survival (OS) was not reported or assessed in this CSR.

Comment: In a retrospective meta-analysis of patients with resected Stage II/III melanoma, RFS was assessed to be a valid surrogate for OS using data from adjuvant studies with interferon or a checkpoint inhibitor (ipilimumab).[10][11]

The conclusion from the latter publication was that in high-risk Stage II-III melanoma, in future adjuvant studies a Hazard Ratio for RFS of 0.77 or less would predict a treatment impact on OS.

7.2.1.5. Randomisation and blinding methods

Eligible subjects were randomised in a 1:1 ratio, to either nivolumab or ipilimumab treatment group by IVRS using a permuted block design. The reasons for non-randomisation were:

No longer met study criteria n = 309 (24.4%); withdrew consent n = 37(2.9%); poor/non-compliance n = 2 (0.2%); administrative reason by sponsor n = 1(< 0.1%); other n = 9 (0.7%).

Randomisation was stratified according to American Joint Committee on Cancer (AJCC) disease stage at study entry (Stage IIIB/C versus Stage IV M1a-M1b versus Stage IV M1c) and tumour PD-L1 status (positive (expression level > 5%) versus negative (expression level < 5%)/indeterminate), centrally tested, at baseline.

As noted above, placebo treatments using the treatment schedule for the non-randomised active were utilised in both arms.

Subjects, investigator, site staff and Bristol-Myers Squibb (BMS) were blinded to the study drug administered (nivolumab plus placebo or ipilimumab plus placebo). Each investigative site assigned an unblinded pharmacist/designee, and an unblinded site monitor was assigned by BMS to provide oversight of drug supply and other unblinded study documentation. The sponsor central study team and the investigative clinical site staff were blinded to results from PD-L1 analysis.

There were no cases of accidental unblinding. *As of the 15-May-2017 clinical cut-off for this analysis, there were 269 subjects whose treatment was unblinded to the site only after disease recurrence to determine subsequent treatment (with approval from the Medical Monitor) and 15 cases of unblinding for safety reasons. CSR*

The subject status summary information, Table 6 below, lists n = 222 with disease recurrence as the reason for not continuing in treatment period. The above statement indicates that another 47 subjects were unblinded for disease recurrence after completion of treatment.

[10]Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. N Engl J Med 2016; 375:1845-55

[11]Suciu S et al Relapse-free Survival as a surrogate for Overall Survival in the evaluation of Stage II-III melanoma Adjuvant Therapy JNatl Cancer Inst (2018) 110(1) doi:10.93/jcni/djx133

Table 6: Patient Disposition

Status (%)	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg	Total
ENROLLED			1264
SUBJECTS RANDOMIZED	453	453	906
SUBJECTS NOT TREATED (%)	1 (0.2)	0	1 (0.1)
REASON FOR NOT BEING TREATED (%)			
SUBJECT WITHDREW CONSENT	1 (0.2)	0	1 (0.1)
SUBJECTS TREATED	452	453	905
CONTINUING IN THE TREATMENT PERIOD	0	0	0
NOT CONTINUING IN THE TREATMENT PERIOD	452 (100.0)	453 (100.0)	905 (100.0)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD			
DISEASE RECURRENCE	121 (26.8)	101 (22.3)	222 (24.5)
STUDY DRUG TOXICITY	41 (9.1)	208 (45.9)	249 (27.5)
ADVERSE EVENT UNRELATED TO STUDY DRUG	5 (1.1)	5 (1.1)	10 (1.1)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	5 (1.1)	9 (2.0)	14 (1.5)
SUBJECT WITHDREW CONSENT	2 (0.4)	3 (0.7)	5 (0.6)
POOR/NON-COMPLIANCE	0	1 (0.2)	1 (0.1)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1 (0.2)	1 (0.1)
OTHER	3 (0.7)	3 (0.7)	6 (0.7)
COMPLETED	275 (60.8)	122 (26.9)	397 (43.9)
CONTINUING IN THE STUDY	393 (86.9)	379 (83.7)	772 (85.3)
NOT CONTINUING IN THE STUDY	59 (13.1)	74 (16.3)	133 (14.7)
REASON FOR NOT CONTINUING IN THE STUDY			
DEATH	44 (9.7)	45 (9.9)	89 (9.8)
SUBJECT WITHDREW CONSENT	13 (2.9)	23 (5.1)	36 (4.0)
LOST TO FOLLOW-UP	2 (0.4)	3 (0.7)	5 (0.6)
OTHER	0	3 (0.7)	3 (0.3)

Percentages based on subjects entering treatment period

7.2.1.6. Analysis populations

There were 1264 subjects enrolled. Once enrolled via IVRS, subjects who met all eligibility criteria were randomised 1:1 to nivolumab or ipilimumab, as above. All 906 randomised subjects were the primary population used for the primary efficacy analysis. In the nivolumab arm n = 453; ipilimumab: n = 453.

The all-treated population, all randomised patients who received at least one dose of study drug, n = 905, was the population for safety and dosing analyses.

There were 905 PD-L1-tested subjects of whom 867 were 'PD-L1 evaluable' that is, had quantifiable PD-L1 expression; 427 in nivolumab and 440 in ipilimumab treatment groups.

For immunogenicity testing, 426 nivolumab and 405 ipilimumab subjects were evaluable, that is, had baseline and at least one post-baseline assessment for ADA.

7.2.1.7. Sample size

The primary objective of the study was to compare RFS between the treatment arms in all randomised subjects. RFS was evaluated for a treatment effect at an overall alpha level of 0.05 (two-sided) with approximately 85% power. The number of events and power were calculated assuming a delayed treatment effect and cure fraction. Approximately 800 subjects total were to be randomised to the two treatment arms in a 1:1 ratio; a total of 906 subjects were actually randomised.

7.2.1.8. Statistical methods

Discrete variables were tabulated by the frequency and proportion of subjects falling into each category, grouped by treatment. Continuous variables were summarised by treatment using the mean, standard deviation, median, minimum and maximum values.

Time-to-event distributions were estimated using Kaplan-Meier techniques. This was done for endpoints of RFS and DMFS. Median survival times along with 95% CIs were constructed based on a log-log transformed CI for the survivor function S(t). The primary RFS analyses were conducted in all randomised subjects using a two-sided log-rank test stratified by PD-L1 status and Stage at study entry as recorded in the IVRS. The hazard ratio and corresponding two-sided (1-adjusted α) % CI was estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors.

RFS curves, RFS medians with 95% CIs, and RFS rates at 6, 12, and 18 months with 95% CIs were estimated using Kaplan-Meier methodology.

To evaluate PD-L1 expression as a predictive biomarker, a Cox proportional hazards model was used to test the interaction between PD-L1 expression (positive versus negative) and treatment arm for the RFS endpoint. Additionally, RFS was analysed within each PD-L1 expression subgroup (positive and negative) including hazard ratios with corresponding confidence intervals. RFS curves and medians estimated using Kaplan-Meier methodology were descriptive and not adjusted for multiplicity.

Approximately 450 RFS events were anticipated at the final RFS analysis, ensuring at least 85% power to detect a hazard ratio of 0.75 with an overall type I error of 0.05 (two-sided).

Taking into account the actual AJCC disease stage distribution (approximately 80% were Stage IIIB/C), the assumptions in the protocol were re-evaluated and the event rate was found to be significantly lower than anticipated in the original protocol. The likelihood of reaching the expected number of 450 RFS events at 36 months of follow up (the original time-based analysis) was considered to be exceedingly low.

A protocol amendment in January 2017 specified that an interim analysis would be conducted after all subjects had a minimum of 18 months of follow-up, with a final analysis still occurring at 36 months of follow-up. Approximately 350 RFS events were anticipated at this interim analysis. If the RFS was significant the trial was to continue and the OS will be tested hierarchically. One formal OS interim analysis will allow for early stopping for superiority.

As of the data cut-off for this interim analysis, 360 of the planned 450 RFS events (80% information fraction) had occurred with a minimum follow-up of approximately 18 months. The stopping boundary at this interim analysis was derived based on the 360 RFS events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. The critical HR was 0.78 with an adjusted alpha level of 0.0244 (two-sided). The type I error to be used for final RFS analysis would have been 0.043 (two-sided).

An independent Data Monitoring Committee (DMC) met on 30-Jun-2017 to review the formal interim analysis of RFS as specified in the Study CA209238 protocol. The DMC confirmed that the pre-specified boundary for RFS (nominal significance level $p < 0.0244$) was crossed, with no new safety signals.

7.2.1.9. Participant flow

Of 906 subjects randomised (453 to nivolumab, 453 to ipilimumab), 905 (99.9%) were treated (452 with nivolumab, 453 with ipilimumab).

There were 10 sites in Australia, with 78 patients randomised across these sites, 8.6% of the total randomised study subjects.

The reasons for 'discontinuation of treatment' prior to completion of the study were specified in the protocol.

The primary reason for not continuing in the treatment period in the nivolumab group was treatment completion (that is, completed the protocol-specified maximum treatment duration of 1 year) n = 275 (60.8%), versus 122 (26.9%) in the ipilimumab group.

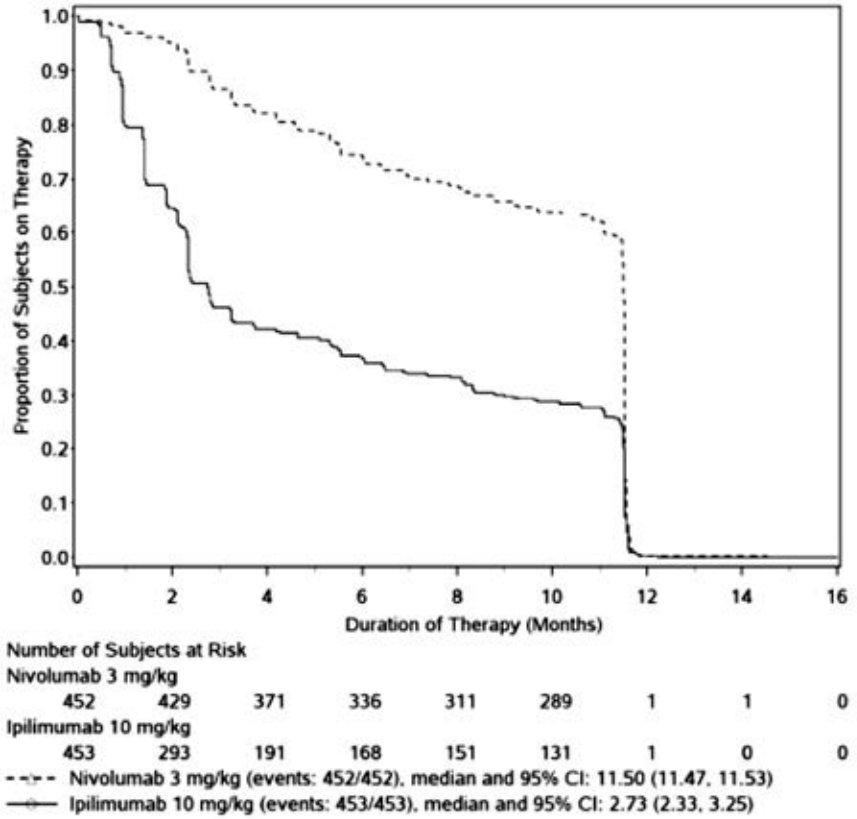
In contrast, study drug toxicity was the commonest reason for not continuing in the ipilimumab group; 208 (45.9%) versus 41(9.1%) in the nivolumab group.

As of the 12 June 2017 database lock, all subjects in both treatment groups had discontinued study treatment. See Table 6.

The median duration of therapy was 11.50 months in the nivolumab group and 2.73 months in the ipilimumab group.

As seen from K-M curve below, showing exposure to study therapy , after the first month the proportion of subjects still on therapy was higher at every time point in the nivolumab group than in the ipilimumab group.

Figure 3: Kaplan-Meier Plot of duration of study therapy; All treated subjects



The reason for not continuing in the treatment period was 'Disease recurrence' for 26.8% in the nivolumab group and 22.3% in the ipilimumab group.

In the nivolumab group 393 subjects (86.9%) were continuing in the study versus 379 (83.7%) in the ipilimumab group.

Of 133 subjects not continuing in the study, in the nivolumab group 44/59 died (9.7% of total) versus 45/74 in the ipilimumab group (9.9% of total).

The status of patients at clinical cut-off for the interim CSR is summarised as follows:

Table 7: Patient status at clinical cut-off for the interim study

Status (%)	Nivolumab 3mg/kg N = 453	Ipilimumab 10 mg/kg N = 453	Total N=906
Enrolled			1264
Not randomised			358
Randomised	453	453	906
Not treated –withdrew consent (%)	1 (0.2)	0	1 (0.2)

Status (%)	Nivolumab 3mg/kg N = 453	Ipilimumab 10 mg/kg N = 453	Total N=906
Subjects treated	452	453	905
Continuing in the treatment period	0	0	0
Not continuing in the treatment period	452 (100)	453 (100)	905 (100)
Reasons for not continuing treatment			
Disease recurrence	121 (26.8)	101 (22.3)	222 (24.5)
Study drug toxicity	41 (9.1)	208 (45.9)	249 (27.5)
AE unrelated to study drug	5 (1.1)	5 (1.1)	10 (1.1)
Subject request	5(1.1)	9(2.0)	14 (1.5)
Withdrew consent	2 (0.4)	3 (0.7)	5(0.6)
Poor/non-compliance	0	1 (0.2)	1 (0.1)
No longer met criteria	0	1 (0.2)	1 (0.1)
Other	3 (0.7)	3 (0.7)	6 (0.7)
Completed	275 (60.8)	122 (26.9)	397 (43.9)
Continuing in the study	393 (86.9)	379 (83.7)	772(85.3)
Not continuing	59 (13.1)	74(16.3)	133 (14.7)
Reason not continuing			
Death	44 (9.7)	45 (9.9)	89 (9.8)
Withdrew consent	13 (2.9)	23 (5.1)	36 (4.0)
Lost to follow-up	2 (0.4)	3 (0.7)	5 (0.6)
Other	0	3 (0.7)	3 (0.7)

Subjects who discontinued treatment for reasons other than recurrence were to continue to have surveillance assessments until local, regional, or distant recurrence (whichever comes first) for Stage IV subjects and until distant recurrence for Stage III subjects.

For subsequent anti-cancer therapy see Table 8 below.

Table 8: Subsequent cancer therapy summary All randomised subjects

	Number of Subjects (%)	
	Nivolumab 3 mg/kg N = 453	Ipilimumab 10 mg/kg N = 453
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	129 (28.5)	171 (37.7)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	24 (5.3)	26 (5.7)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	69 (15.2)	64 (14.1)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%) (5 or MORE SUBJECTS in EITHER GROUP)	90 (19.9)	136 (30.0)
IMMUNOTHERAPY	50 (11.0)	104 (23.0)
IPILIMUMAB	35 (7.7)	15 (3.3)
NIVOLUMAB	17 (3.8)	43 (9.5)
PEMBROLIZUMAB	10 (2.2)	63 (13.9)
BRAF INHIBITOR	41 (9.1)	40 (8.8)
DABRAFENIB	30 (6.6)	30 (6.6)
VEMURAFENIB	16 (3.5)	14 (3.1)
MEK/NRAS INHIBITOR	31 (6.8)	40 (8.8)
COBIMETINIB	10 (2.2)	13 (2.9)
TRAMETINIB	22 (4.9)	27 (6.0)
OTHER SYSTEMIC CANCER THERAPY - CHEMOTHERAPY	25 (5.5)	24 (5.3)
CARBOPLATIN	5 (1.1)	3 (0.7)
DACARBAZINE	14 (3.1)	8 (1.8)
PACLITAXEL	6 (1.3)	3 (0.7)
TALIMOGENE LAHERPAREPVEC	2 (0.4)	5 (1.1)

(1) Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if subject never treated).

In the nivolumab arm 129 (28.5%) of subjects received subsequent anti-cancer therapy, compared to 171 (37.7%) in the ipilimumab arm.

Immunotherapy was the subsequent anti-cancer therapy received by 50 (11%) nivolumab and 104 (23%) ipilimumab subjects. Immunotherapy included pembrolizumab, nivolumab, and ipilimumab monotherapy, interferon and ipilimumab/nivolumab combinations.

7.2.1.10. Major protocol violations/deviations

The CSR states '*After review of the reported protocol deviations, it was determined there was no impact on the interpretability of the study results.' CSR 238 page 57*

According to the CSR, '*relevant' protocol deviations were 'significant protocol deviations that could potentially affect the interpretability of study results'*.

The evaluator was initially unable to locate the rationale or criteria for considering significant protocol deviations as 'relevant', as specified in the protocol; details of 'relevant programmable deviations', are copied below:

Relevant protocol deviations

The following programmable deviations will be considered as relevant protocol deviations and be summarized by treatment group and overall for all randomized subjects. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

At Entrance:

- No histologically documented stage IIIb or stage IIIc or stage IV melanoma as per AJCC staging
- Documented/confirmed disease at baseline
- Subject with baseline ECOG performance status > 1

- The last intervention demonstrating that the subject is free of disease is more than 13 weeks prior to randomization
- Subject received prior systemic anti-cancer therapy (prior treatment with adjuvant interferon is allowed if completed > 6 months prior to randomization)
- Subject with ocular/uveal melanoma

On-study:

- Subjects receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of cancer) while on study therapy
- Subjects treated differently than as randomized (subjects who received the wrong treatment, excluding the never treated)

Relevant protocol deviations were reported in 33 subjects (3.6%); 12 in the nivolumab arm (2.6%) and 21 in the ipilimumab arm (4.6%). See Table 9 below:

Table 9: Relevant protocol deviations

	Number of Subjects (%)		
	Nivolumab 3 mg/kg N = 453	Ipilimumab 10 mg/kg N = 453	Total N = 906
SUBJECTS WITH AT LEAST ONE DEVIATION	12 (2.6)	21 (4.6)	33 (3.6)
AT ENTRY			
THE LAST INTERVENTION DEMONSTRATING THE SUBJECT IS FREE OF DISEASE IS MORE THAN 13 WEEKS PRIOR TO RANDOMIZATION	4 (0.9)	12 (2.6)	16 (1.8)
NO HISTOLOGICALLY DOCUMENTED STAGE IIIB OR STAGE IIIC OR STAGE IV MELANOMA AS PER AJCC STAGING	4 (0.9)	0	4 (0.4)
DOCUMENTED/CONFIRMED DISEASE AT BASELINE	1 (0.2)	2 (0.4)	3 (0.3)
SUBJECT RECEIVED PRIOR SYSTEMIC ANTI-CANCER THERAPY	0	4 (0.9)	4 (0.4)
ON-STUDY			
SUBJECTS RECEIVING ANTI-CANCER THERAPY WHILE ON STUDY THERAPY	3 (0.7)	3 (0.7)	6 (0.7)

At study entry the most common relevant protocol deviation was that the last intervention demonstrating the subject was free of disease was more than 13 weeks prior to randomisation. This occurred in 4 subjects (0.9%) randomised to the nivolumab arm and 12 subjects (2.6%) in the ipilimumab arm.

There were 4 patients with no histologically documented Stage IIIB/C or Stage IV melanoma randomised to nivolumab, versus 0 in the ipilimumab arm.

One nivolumab and 2 ipilimumab subjects did not have documented/confirmed disease at baseline; 4 nivolumab subjects had received prior systemic anti-cancer therapy.

On-study, concurrent anti-cancer therapy was considered a relevant protocol deviation.

In both study arms, 3 subjects (0.7%) received concurrent anti-cancer therapy while on study therapy.

A sensitivity analysis of RFS was included in the SAP as follows:

> *RFS analysis for subjects with no relevant deviation: This analysis will be conducted only if there are more than 10% of subjects with relevant protocol deviations.*
>
> *A comparison of RFS between the two treatment arms using a 2-sided, stratified log rank test will be conducted in which recurrence-free subjects who are lost to follow-up for any*

cause will be considered as having an event at the time of the last tumour assessment date prior to loss to follow-up.

A sensitivity analysis was performed for interim study; see *RFS Sensitivity analyses* below.

Comments*:* Accuracy of ascertainment of melanoma stage and 'No Evidence of Disease' for those randomised appears critical to internal validity for this adjuvant study.

The CSR shows by-subject listing of eligibility criteria for all enrolled subjects. The majority who failed criteria were not randomised.

It is unclear why a small number of subjects were randomised in spite of failing inclusion/exclusion criteria. No additional sponsor comment was located regarding the randomisation of these subjects.

The sponsor was asked for any additional information regarding randomisation of subjects who failed inclusion/exclusion criteria.

All significant protocol deviations were provided and these were reviewed.

The evaluator was unable to locate criteria in the protocol for considering significant protocol deviations as 'relevant' with respect to interpretability of efficacy.

In general those listed as 'relevant' were deviations that might affect the ascertainment of original melanoma stage, of the status of 'no evidence of disease', and treatment with other anti-cancer treatments.

Other protocol violations such as one missing scan, 'out of window' scan timing, AEs not reported within specified timeframes, and individual lab tests not reported, appeared less likely to influence the outcome with respect to efficacy.

The numbers affected by 'relevant' protocol deviations as seen in Table 9 were a small proportion of those randomised.

The sponsor was asked to direct the evaluator to the rationale and/or criteria for specification of significant protocol deviations as 'relevant'.

7.2.1.11. Baseline data

Demographic

For all randomised subjects, the mean age in the nivolumab arm was 54.4 years (range 19-83), ipilimumab 53.6 years (range 18-86); median age overall was 55.0 years. In both groups around 25 % were over the age of 65 years. The majority of subjects were White (94.8%) and male (58.2%).

Of the 906 randomised subjects, 523 (57.7%) were in Europe, 257 (28.4%) were in North America, and 126 (13.9%) were in Rest of World.

Study sites in Australia had 78 randomised subjects, 8.6% of the total; 34 in the nivolumab arm and 44 in the ipilimumab arm.

Demographic characteristics were reasonably balanced between treatment arms.

Disease characteristics

Disease stage at study entry (Stage IIIB/C versus Stage IV M1a-M1b versus Stage IV M1c) and baseline tumour PD-L1 expression status (positive (at 5% cut-off) versus negative/indeterminate) were stratification factors based on information as recorded in the IVRS.

At baseline, ECOG performance status was 0 (90.3%) or 1 (9.7%). For nivolumab, 413 subjects (91.2%) had ECOG 0 versus ipilimumab 405 (89.4%).

For some disease characteristics at baseline there were slight imbalances; see Table 10.

Table 10: Study 238 Baseline Disease Characteristics

	Nivolumab 3 mg/kg N = 453	Ipilimumab 10 mg/kg N = 453	Total N = 906
PERFORMANCE STATUS (ECOG) [%]			
0	413 (91.2)	405 (89.4)	818 (90.3)
1	40 (8.8)	48 (10.6)	88 (9.7)
TIME FROM SURGICAL RESECTION TO RANDOMIZATION (WEEKS)			
N	453	453	906
MEAN	8.8	9.1	9.0
MEDIAN	9.0	9.7	9.3
MIN , MAX	0 , 15	0 , 35	0 , 35
Q1 , Q3	6.9 , 11.3	7.0 , 11.6	7.0 , 11.3
STANDARD DEVIATION	2.63	3.20	2.93
< 3	5 (1.1)	17 (3.8)	22 (2.4)
3- < 6	60 (13.2)	49 (10.8)	109 (12.0)
6- < 9	156 (34.4)	126 (27.8)	282 (31.1)
9- < 12	180 (39.7)	180 (39.7)	360 (39.7)
12- < 15	50 (11.0)	76 (16.8)	126 (13.9)
15- < 18	2 (0.4)	3 (0.7)	5 (0.6)
18- < 21	0	1 (0.2)	1 (0.1)
>= 21	0	1 (0.2)	1 (0.1)
CRF DISEASE STAGE AT STUDY ENTRY			
STAGE IIIB	163 (36.0)	148 (32.7)	311 (34.3)
STAGE IIIC	204 (45.0)	218 (48.1)	422 (46.6)
STAGE IV	82 (18.1)	87 (19.2)	169 (18.7)
OTHER[A]	2 (0.4)	0	2 (0.2)
NOT REPORTED	2 (0.4)	0	2 (0.2)
TUMOR ULCERATION STATUS IN STAGE III SUBJECTS			
ABSENT	201 (44.4)	216 (47.7)	417 (46.0)
PRESENT	153 (33.8)	135 (29.8)	288 (31.8)
NOT REPORTED	15 (3.3)	15 (3.3)	30 (3.3)
LYMPH NODE INVOLVEMENT IN STAGE III SUBJECTS			
MICROSCOPIC	125 (27.6)	134 (29.6)	259 (28.6)
MACROSCOPIC	219 (48.3)	214 (47.2)	433 (47.8)
NOT REPORTED	25 (5.5)	18 (4.0)	43 (4.7)
CLASSIFICATION OF NODES IN STAGE III SUBJECTS			
IN TRANSIT MET/SATELLITES W/O MET NODES	85 (18.8)	75 (16.6)	160 (17.7)
MATTED NODES	63 (13.9)	67 (14.8)	130 (14.3)
IN TRANSIT MET/SATELLITES W/ MET NODES	82 (18.1)	86 (19.0)	168 (18.5)
NOT REPORTED	139 (30.7)	138 (30.5)	277 (30.6)

Table 10 continued: Study 238 Baseline Disease Characteristics

	Nivolumab 3 mg/kg N = 453	Ipilimumab 10 mg/kg N = 453	Total N = 906
M-STATUS IN STAGE IV SUBJECTS			
M1A	50 (11.0)	51 (11.3)	101 (11.1)
M1B	12 (2.6)	15 (3.3)	27 (3.0)
M1C WITH BRAIN METASTASES	6 (1.3)	6 (1.3)	12 (1.3)
M1C WITHOUT BRAIN METASTASES	14 (3.1)	15 (3.3)	29 (3.2)
MELANOMA SUBTYPE			
MUCOSAL	16 (3.5)	13 (2.9)	29 (3.2)
CUTANEOUS	388 (85.7)	378 (83.4)	766 (84.5)
ACRAL	16 (3.5)	17 (3.8)	33 (3.6)
OCULAR/UVEAL	0	0	0
OTHER	33 (7.3)	45 (9.9)	78 (8.6)
TUMOR ORIGIN			
PRIMARY	241 (53.2)	215 (47.5)	456 (50.3)
RECURRENT	208 (45.9)	235 (51.9)	443 (48.9)
NOT REPORTED	4 (0.9)	3 (0.7)	7 (0.8)
BASELINE LDH 1			
<= ULN	413 (91.2)	411 (90.7)	824 (90.9)
> ULN	32 (7.1)	37 (8.2)	69 (7.6)
NOT REPORTED	8 (1.8)	5 (1.1)	13 (1.4)
BASELINE LDH 2			
<= 2*ULN	445 (98.2)	446 (98.5)	891 (98.3)
> 2*ULN	0	2 (0.4)	2 (0.2)
NOT REPORTED	8 (1.8)	5 (1.1)	13 (1.4)
CRF PD-L1 STATUS 1			
< 1%	140 (30.9)	133 (29.4)	273 (30.1)
>= 1%	287 (63.4)	307 (67.8)	594 (65.6)
INDETERMINATE	25 (5.5)	13 (2.9)	38 (4.2)
UNEVALUABLE/NOT REPORTED	1 (0.2)	0	1 (0.1)
CRF PD-L1 STATUS 2			
< 5%	275 (60.7)	286 (63.1)	561 (61.9)
>= 5%	152 (33.6)	154 (34.0)	306 (33.8)
INDETERMINATE	25 (5.5)	13 (2.9)	38 (4.2)
UNEVALUABLE/NOT REPORTED	1 (0.2)	0	1 (0.1)
CRF PD-L1 STATUS 3			
< 10%	321 (70.9)	335 (74.0)	656 (72.4)
>= 10%	106 (23.4)	105 (23.2)	211 (23.3)
INDETERMINATE	25 (5.5)	13 (2.9)	38 (4.2)
UNEVALUABLE/NOT REPORTED	1 (0.2)	0	1 (0.1)
B-RAF MUTATION STATUS			
MUTANT	187 (41.3)	194 (42.8)	381 (42.1)
WILDTYPE	197 (43.5)	214 (47.2)	411 (45.4)
NOT REPORTED	69 (15.2)	45 (9.9)	114 (12.6)

Time from surgical resection

The median time from surgical resection to randomisation was 9.3 weeks (range: 0 to 35 weeks); 85.3% of the subjects were randomised within 12 weeks of resection.

- More subjects in the ipilimumab arm had greater than 12 weeks from surgical resection to randomisation; 81 (17.9%) versus 52 (11.5%).

Melanoma subtype

Melanoma was of the cutaneous subtype in 84.5% of the subjects; 388 (85.7%) in nivolumab arm versus 478 (83.4%) in the ipilimumab arm.

Less than 20 in each group had mucosal melanoma, and similar numbers were enrolled with acral melanoma.

In the nivolumab group 33 (7.3%) subjects had melanoma classified as 'other' versus 45 (9.9%) for ipilimumab.

Melanoma Disease Stage

From CRF, overall 34.3% of subjects had Stage IIIB, 46.6% had Stage IIIC, and 18.7% had Stage IV disease.

- In the nivolumab arm the numbers were 163 (36%), 204 (45%), and 82 (18.1%) with Stage IIIB, Stage IIIC, and Stage IV disease, respectively. In the nivolumab arm two subjects were enrolled who had disease Stage IIIA.

- In the ipilimumab arm there were 148 (32.7%), 218 (48.1%) and 87(19.2%) with Stage IIIB, Stage IIIC, and Stage IV disease, respectively.

Tumour origin

Tumour origin was

- Primary in 50.3% of subjects (53.2% for nivolumab arm versus 47.5 % in ipilimumab arm)
- Recurrent in 48.8 % (45.9% nivolumab versus 51.9% ipilimumab).

PD-L1 expression

Tumour PD-L1 expression < 5% and ≥ 5% was 275 (60.7%) and 152 (33.6%) respectively for nivolumab versus 286 (63.1%) and 154 (34.0%) for ipilimumab; overall 4.2% of the subjects were indeterminate, 25 in nivolumab arm versus 13 in ipilimumab.

Other

Of all randomised subjects, 42.1% were BRAF V600 mutation positive, 45.4% were BRAF wild type; for 12.6% BRAF status was unknown. In the nivolumab group 187(41.3%) were B-RAF mutant, 197(43.5%) wildtype and 69(15.2%) unknown, versus 192(42.8%), 214 (47.2%) and 45 (9.9%) respectively for the ipilimumab group.

Prior radiotherapy had been received by 11 subjects (2.4%) in both nivolumab and ipilimumab arms; systemic cancer therapy had been received by 17 (3.8%) in the ipilimumab arm versus 13 (2.9%) in nivolumab arm.

With respect to timeliness of study treatment, 94.9% of treated subjects in both groups received the first dose of treatment within 3 days of randomisation.

Comment: The CSR described patient demographics and baseline characteristics as 'comparable' or 'generally balanced' between treatment groups.

The nivolumab arm had greater frequencies of some characteristics and/or missing data. However the differences in frequencies between treatment arms were generally less than 5% for each characteristic.

7.2.1.12. Results for the primary efficacy outcome

Recurrence-Free Survival

RFS was defined as the time between the date of randomisation and the date of first recurrence (local, regional or distant metastasis, confirmed by pathology and/or imaging), new primary melanoma, or death (whatever the cause), whichever occurs first.

As of the data cut-off for this interim analysis, 360 of the estimated expected 450 RFS events (80% information fraction) had occurred.

On 30-Jun-2017 the DMC met to review the formal interim analysis of RFS specified in the Study CA209238 protocol, and confirmed that the pre-specified boundary for RFS, 0.78 (nominal significance level $p < 0.0244$) was crossed, with no new safety signals.

The summary below for the primary endpoint is copied from the CSR. There were 154 events for 453 subjects in the nivolumab arm (34%) versus 206 events in 453 subjects in the ipilimumab arm (45.5%).

Table 11: Summary of efficacy results; All randomised subjects

	Nivolumab 3 mg/kg (N = 453)	Ipilimumab 10 mg/kg (N = 453)
PRIMARY ENDPOINT		
Recurrence-free Survival (RFS)		
Events, n (%)	154 (34.0)	206 (45.5)
Median RFS (95% CI)[a], months	N.A.	N.A. (16.56, N.A.)
hazard ratio (HR) (97.56% CI)[b]	0.65 (0.51, 0.83)	
Stratified log rank p-value[c]	<0.0001	
Rate at 12 months, % (95% CI)[a]	70.5 (66.1, 74.5)	60.8 (56.0, 65.2)
Rate at 18 months, % (95% CI)[a]	66.4 (61.8, 70.6)	52.7 (47.9, 57.4)

Median RFS was not reached for either treatment arm.

The primary analysis in all randomised subjects demonstrated statistically significant improvement in RFS as assessed by investigators in patients treated with nivolumab 3 mg/kg as adjuvant therapy compared to ipilimumab 10 mg/kg; HR = 0.65 (97.56% CI: 0.51, 0.83), (stratified log-rank $p < 0.0001$), in the enrolled population with completely resected Stage IIIB, IIIC c or Stage IV melanoma.

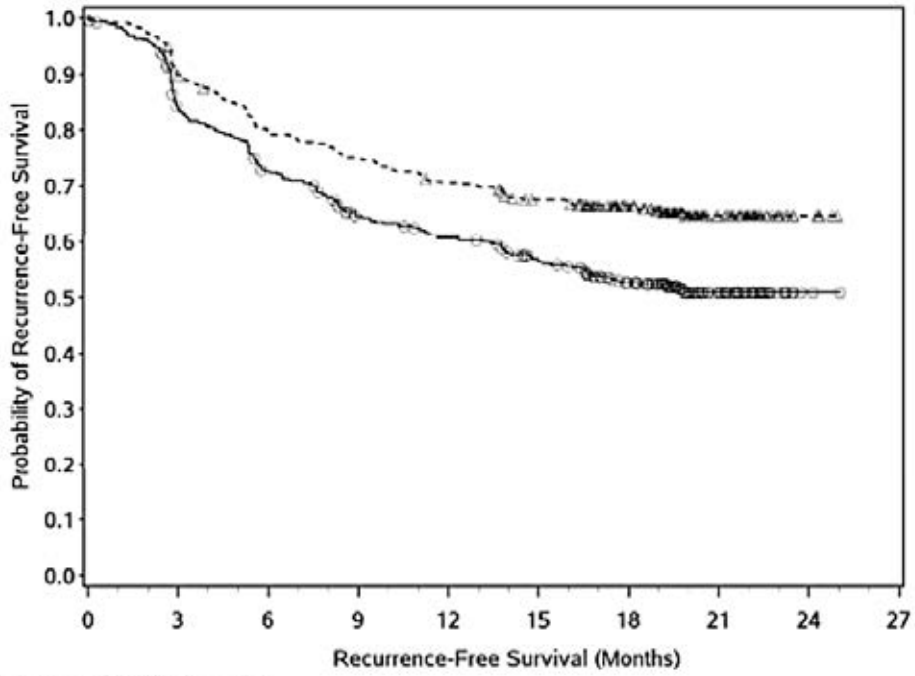
Estimated RFS rates were higher in the nivolumab group than in the ipilimumab group:

- 6 months (79.8% versus 72.6%),
- 12 months (70.5% versus 60.8%),
- 18 months (66.4% versus 52.7%).

The minimum follow up to clinical cut-off date 15.5.2017 for all randomised subjects was approximately 18 months. Estimation of Median and range for duration of follow-up was not located in the CSR and the sponsor was asked to clarify this for the interim study.

Kaplan–Meier curves for RFS separated after three months, favouring nivolumab, as seen below.

Figure 4: Kaplan-Meier Recurrence free survival plot; All randomised subjects



Number of Subjects at Risk

Nivolumab 3 mg/kg									
453	399	353	332	311	291	249	71	5	0
Ipilimumab 10 mg/kg									
453	364	314	269	252	225	184	56	2	0

Nivolumab 3 mg/kg (events: 154/453), median and 95% CI: N.A.
Ipilimumab 10 mg/kg (events: 206/453), median and 95% CI: N.A. (16.56, N.A.)
Hazard Ratio (Nivo 3 mg/kg over Ipi 10 mg/kg) and 97.56% CI (1): 0.65 (0.51, 0.83)
Stratified log-rank p-value: <0.0001

As recorded in the CSR, time from last disease assessment date to clinical data cut-off was within 3 months for 431 (95.1%) subjects in the nivolumab group and 418 (92.3%) in the ipilimumab group.

The Reasons for censoring RFS is shown below in full at Table 12.

Table 12: Study CA209238 Reason for censoring, RFS at time of data base lock

	Nivolumab 3 mg/kg N = 453	Ipilimumab 10 mg/kg N = 453
NUMBER OF EVENTS (%)	154 (34.0)	206 (45.5)
TYPE OF EVENTS (%)		
RECURRENCE	154 (34.0)	201 (44.4)
DISEASE AT BASELINE	1 (0.2)	2 (0.4)
LOCAL RECURRENCE	30 (6.6)	44 (9.7)
REGIONAL RECURRENCE	31 (6.8)	34 (7.5)
DISTANT METASTASIS	85 (18.8)	117 (25.8)
NEW PRIMARY MELANOMA	7 (1.5)	4 (0.9)
DEATH	0	5 (1.1)
NUMBER OF SUBJECTS CENSORED (%)	299 (66.0)	247 (54.5)
CENSORED ON DATE OF RANDOMIZATION	2 (0.4)	7 (1.5)
NO BASELINE DISEASE ASSESSMENT (1)	1 (0.2)	0
NEVER TREATED	0	0
OTHER	1 (0.2)	0
NO ON-STUDY DISEASE ASSESSMENT WITH EITHER NO RECURRENCE/DEATH OR RECURRENCE/DEATH WITH PRIOR SUBSEQUENT THERAPY/SECOND NON-MELANOMA PRIMARY CANCER (1)	1 (0.2)	7 (1.5)
NEVER TREATED	1 (0.2)	0
RECURRENCE/DEATH WITH PRIOR SUBSEQUENT ANTI CANCER THERAPY	0	0
RECURRENCE/DEATH WITH PRIOR SECOND NON-MELANOMA PRIMARY CANCER	0	0
NO RECURRENCE/DEATH	0	7 (1.5)

Table 12 continued: Study CA209238 Reason for censoring, RFS at time of data base lock

	Nivolumab 3 mg/kg N = 453	Ipilimumab 10 mg/kg N = 453
CENSORED ON DATE OF LAST DISEASE ASSESSMENT ON-STUDY/ OR LAST ASSESSMENT PRIOR TO SUBSEQUENT ANTI CANCER THERAPY/ SECOND NON-MELANOMA PRIMARY CANCER	297 (65.6)	240 (53.0)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (2)	4 (0.9)	10 (2.2)
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	0	7 (1.5)
RECEIVED SUBSEQUENT RADIOTHERAPY	1 (0.2)	0
RECEIVED SUBSEQUENT SURGERY	3 (0.7)	3 (0.7)
SECOND NON-MELANOMA PRIMARY CANCER (2)	1 (0.2)	4 (0.9)
STILL ON TREATMENT	0	0
IN FOLLOW-UP	286 (63.1)	215 (47.5)
OFF STUDY	6 (1.3)	11 (2.4)
LOST TO FOLLOW-UP	0	0
SUBJECT WITHDREW CONSENT	6 (1.3)	9 (2.0)
OTHER	0	2 (0.4)

(1) Disease assessments and death if any, occurring after start of subsequent anti-cancer therapy or second non-melanoma primary cancer are not considered.
(2) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy or experienced second non-melanoma primary cancer without a prior reported RFS event. Those subjects were censored at the last evaluable disease assessment prior to/on start date of subsequent anti-cancer therapy or second non-melanoma primary cancer.

Details of events

Nivolumab arm

The 154 events in the nivolumab arm were all 'recurrences'.

These events comprised

- 1 subject who had disease at baseline
- 30 (6.6%) with local recurrence
- 31 (6.8%) with regional recurrence
- 85 (18.8%) with distant metastasis
- 7 subjects (1.5%) with new primary melanoma.

Ipilimumab arm

In the ipilimumab arm there were 206 events.

The events in the ipilimumab arm included 5 deaths.

The 201 'recurrences' comprised

- 2 subjects with disease at baseline
- 44 (9.7%) with local recurrence
- 34 (7.5%) with regional recurrence
- 117 (25.8%) with distant metastasis
- 4 subjects (0.9%) with new primary melanoma.

At the time of the database lock, 299 (66.0%) subjects in the nivolumab group and 247 (54.5%) subjects in the ipilimumab group were censored.

Among those censored, none were still on treatment.

Most were in follow-up; 286 (63.1%) in the nivolumab group and 215 (47.5%) in the ipilimumab group.

Of those censored on date of randomisation, 1 nivolumab subject was never treated, while in the ipilimumab arm 7 subjects had no on-study disease assessment and no recurrence/death.

Of those with disease assessments, in the nivolumab arm 4/297 received subsequent anti-cancer therapy, compared to 10/240 in the ipilimumab arm.

Six subjects treated with nivolumab were off-study versus 11 in the ipilimumab arm; all six nivolumab subjects (1.3%) withdrew consent versus 9 (2.0%) in ipilimumab group.

Mortality rates were similar for both arms by data lock point, around 10%.

The summary table of deaths is copied here from the CSR:

Table 13: Death summary All treated subjects

	Nivolumab 3 mg/kg N = 452	Ipilimumab 10 mg/kg N = 453
NUMBER OF SUBJECTS WHO DIED (%)	44 (9.7)	45 (9.9)
PRIMARY REASON FOR DEATH (%)		
DISEASE	41 (9.1)	41 (9.1)
STUDY DRUG TOXICITY	0	2 (0.4)
UNKNOWN	0	0
OTHER	3 (0.7)	2 (0.4)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	0	0
PRIMARY REASON FOR DEATH (%)		
DISEASE	0	0
STUDY DRUG TOXICITY	0	0
UNKNOWN	0	0
OTHER	0	0
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	3 (0.7)	2 (0.4)
PRIMARY REASON FOR DEATH (%)		
DISEASE	3 (0.7)	1 (0.2)
STUDY DRUG TOXICITY	0	0
UNKNOWN	0	0
OTHER	0	1 (0.2)

Thus it appears there were 7 deaths in total other than those due to recurrences, 3 for nivolumab and 4 for ipilimumab.

From 'Death listing, all enrolled subjects', 7 deaths were identified but no detailed narratives were located. The CSR states 'Safety narratives for deaths within 100 days of the last dose (excluding recurrence) in nivolumab-treated subjects are provided in Table S.6.'

However a table contains narratives for serious AEs. In the table provided, for subjects receiving nivolumab, no narratives were identified as including death.

The summary table copied above shows 3 deaths within 100 days of last dose of nivolumab due to 'disease', taken to mean melanoma 'recurrence', and therefore excluded from safety narratives.

It appears that all 44 deaths in nivolumab arm and n = 40 deaths in ipilimumab arm occurred after the date of first recurrence, and therefore were not RFS events. This is consistent with inspection of the '*By-subject listing of recurrence-free survival, all randomised subjects'* in the CSR.

Comment: The sponsor was asked to confirm that because there were no deaths within 100 days of nivolumab dosing, other than those due to recurrence of pre-randomisation melanoma or new primary melanoma, no safety narratives for deaths appear to be included in the aforementioned table.

The sponsor was asked to direct the evaluator to the location in the dossier of any detailed narratives for deaths in either arm.

The sponsor's response confirmed the above and that there were no narratives for deaths after ipilimumab treatment.

RFS Sensitivity analyses

The sensitivity analyses are copied at Table 14 below.

Table 14: Study CA209238 RFS sensitivity analyses

Sensitivity Analysis	# EVENTS / # SUBJECTS (%) MEDIAN RFS (MONTHS) (1) (95% CI) Nivolumab 3 mg/kg N = 453	Ipilimumab 10 mg/kg N = 453	HR (2) (97.56% CI)	P-Value (3)
RFS (UNSTRATIFIED)	154/453 (34.0) N.A.	206/453 (45.5) N.A. (16.56, N.A.)	0.66 (0.52, 0.84)	<0.0001
RFS STRATIFIED BY PD-L1 STATUS AND DISEASE STAGE PER ECRF/CLINICAL DATABASE	153/448 (34.2) N.A.	206/453 (45.5) N.A. (16.56, N.A.)	0.66 (0.52, 0.83)	<0.0001
RFS ACCOUNTING FOR ASSESSMENT ON/AFTER SUBSEQUENT THERAPY / SECOND NON-MELANOMA PRIMARY CANCER	157/453 (34.7) N.A.	213/453 (47.0) N.A. (16.43, N.A.)	0.65 (0.51, 0.82)	<0.0001
RFS ACCOUNTING FOR MISSING DISEASE ASSESSMENTS PRIOR TO RFS EVENT	152/453 (33.6) N.A.	203/453 (44.8) N.A. (16.56, N.A.)	0.65 (0.51, 0.83)	<0.0001
RFS ACCOUNTING FOR LOST TO FOLLOW-UP	154/453 (34.0) N.A.	207/453 (45.7) N.A. (16.53, N.A.)	0.65 (0.51, 0.82)	<0.0001
RFS FOR SUBJECTS WITH NO RELEVANT DEVIATION	151/441 (34.2) N.A.	196/432 (45.4) N.A. (16.56, N.A.)	0.66 (0.52, 0.84)	0.0001

(1) Based on Kaplan-Meier Estimates.
(2) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab over Ipilimumab.
(3) Log-rank Test stratified by PD-L1 status and disease stage at study entry as entered into the IVRS.
Program Source: /unblinded/bma233672/stats/interim/prog/tables/rt-ef-sens.sas 19JUL2017:07:33:15

Sensitivity analyses, including RFS accounting for subjects lost to follow up, and subjects with no relevant deviations, were consistent with the primary RFS analysis.

Multivariate analysis showed treatment effect adjusted for age, gender, ECOG status, disease stage, PD-L1 status, and time from surgical resection to randomisation (≥ 6 weeks versus < 6 weeks) consistent with primary RFS analysis.

Sub-group analyses

Analysis of RFS results in multiple pre-defined unstratified sub-groups was generally consistent with the primary analysis.

Overall, RFS improvement was seen for nivolumab treated patients compared to ipilimumab across subgroups.

Subgroup analysis by disease stage was as follows:

Table 15: Subgroup analysis by disease stage

Melanoma stage	Nivolumab events/patients	Ipilimumab events/patients	HR (95% CI)
Stage IIIB	41/163	54/148	0.67(0.44-1.00)
Stage IIIC	79/204	109/218	0.65(0.49-0.87)
Stage IVM1a or M1b	25/62	35/66	0.63(0.38-1.05)

Melanoma stage	Nivolumab events/patients	Ipilimumab events/patients	HR (95% CI)
Stage IV M1c	8/20	8/21	1.00(0.37-2.66)

Small subgroups with HR >1 or 95% CI crossing 1 included subjects with melanoma subtype mucosal (n =29, 11 events /16 subjects for nivolumab and 6/13 ipilimumab) and acral (n = 33, recurrence events 13/16 for nivolumab versus 12/17 for ipilimumab); and Stage IV M1C (8/20 versus 8/21), Asian subjects (12/25 versus 10/18), and subjects aged ≥75 years (5/17 versus 7/13).

In the subgroup Stage III with ulceration present plus microscopic lymph node involvement (nivolumab 26 events/66 subjects versus ipilimumab 27events /69 subjects) the HR was 1 (95% CI 0.58, 1.72).

7.2.1.13. Results for other efficacy outcomes

Secondary endpoint: PD-L1 expression and RFS

Baseline PD-L1 expression classification was determined at baseline by central laboratory, and 5% level of PD-L1 expression was used as a stratification factor.

Of 906 randomised subjects, 867 had quantifiable PD-L1 expression in tumour tissue samples collected at baseline; 94.3% of nivolumab subjects versus 97.1% ipilimumab subjects.

The levels of expression were similar in treatment arms; at baseline the stratification factor of 5% or greater PD-L1 expression was found in 152/427 (35.6%) nivolumab subjects versus 154/440 (35%) ipilimumab.

PD-L1 expression 1% or greater than was found in 287/427 (67.2%) nivolumab subjects versus 307/440 (69.8%) ipilimumab; that is, in this study population, around 30% had less than 1% PD-L1 expression.

- Baseline PD-L1 expression was associated with a lower risk of recurrence for nivolumab versus ipilimumab.
- Of note, for subjects with < 1% PD-L1 expression level, the RFS Kaplan-Meier plots were closer for nivolumab and ipilimumab than for cut-off at higher expression levels. However median and upper 95% CI for RFS were not available for nivolumab subjects using this cut-off level with the Kaplan-Meier plots provided.

Overall, the CSR conclusion was that '*subjects treated with nivolumab were considered to have a lower risk of recurrence than those treated with ipilimumab regardless of PD-L1 expression status*'.

- This reflects the protocol (SAP)-specified definition of PD-L1 positive status in this study as > 5% PD-L1 expression.

From Summary of efficacy result Secondary Endpoints in CSR.

Table 16: RFS by baseline PD-L1 expression (5% tumour cell membrane expression)

Nivolumab 3 mg/kg n= 453 kg and Ipilimumab 10 mg/kg n = 453

RFS by Baseline PD-L1 Expression (5% tumor cell membrane expression)		
Subjects with ≥ 5% PD-L1 Expression, n (%)	152 (33.6)	154 (34.0)
Unstratified HR (95% CI)[d]	0.50 (0.32, 0.78)	
Median (95% CI)[a], months	N.A.	N.A.
Subjects with < 5% PD-L1 Expression, n (%)	275 (60.7)	286 (63.1)
Unstratified HR (95% CI)[d]	0.71 (0.56, 0.91)	
Median (95% CI)[a], months	N.A.	15.90 (10.38, N.A.)
Subjects with Non-quantifiable PD-L1 Expression, n (%)	26 (5.7)	13 (2.9)
Unstratified HR (95% CI)[d]	0.78 (0.28, 2.19)	
Median (95% CI)[a], months	N.A. (6.70, N.A.)	N.A. (4.76, N.A.)

Comment: The sponsor concluded that nivolumab-treated subjects have lower risk of recurrence regardless of PD-L1 status. This is based on the definition of PD-L1 positive status as > 5% PD-L1 expression.

It was not clear to the evaluator from the study information why the level of 5% expression was chosen to delineate positive from negative PD-L1 expression in this study.

Almost 70% had PD-L1 ≥1%; in this group the RFS HR (95% CI) provided for nivolumab versus ipilimumab is 0.56 (0.42, 0.73).

However a significant minority of subjects had PD-L1 expression levels < 1%; around 30% of the subjects in this study, consistent with median levels of PD-L1 expression in most regions of 2 to 3.

In this group the nivolumab versus ipilimumab RFS HR (95% CI) provided is 0.82 (0.59, 1.16).

Compared to ipilimumab, nivolumab was associated with lower risk of recurrence for those subjects with any level of PD-L1 expression above 1%.

However, using the cut-off of 5% for positive-negative PD-L1 status determination includes those subjects with PD-L1 expression between 1% and 5% as PD-L1 'negative', together with those with PD-L1 expression of < 1%, for whom the HR shows less certain RFS reduction compared to ipilimumab.

Levels of PD-L1 expression in individual subjects are highly variable:

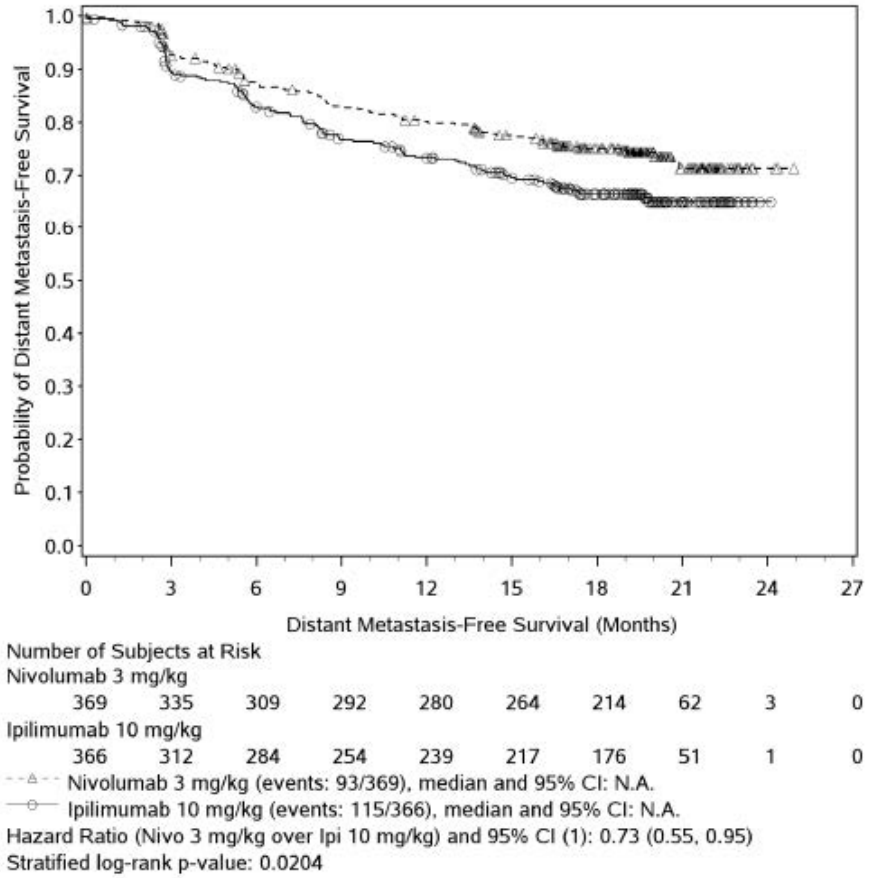
Overall survival estimations were not undertaken in the interim data analysis.

- The sponsor's Clinical summary notes that the survival data were 'not mature' at the time of interim analysis; 89 deaths had occurred.

Exploratory endpoint: Distant metastasis-free survival (DMFS) in subjects with Stage III disease at study entry.

In this subset of subjects the Kaplan-Meier curves also separated after 3 months. See Figure 5.

Figure 5: Kaplan-Meier plot of DMFS; all randomised subjects with Stage III disease



The HR for nivolumab versus ipilimumab for DMFS was 0.73 (95%CI: 0.55, 0.95); stratified log-rank p = 0.0204.

The median DMFS was not reached in either group. The DMFS rates were higher in the nivolumab group than in the ipilimumab group at 6, 12, and 18 month time points.

Table 17: Distant DMFS in subjects with Stage III disease at study entry

Nivolumab 3mg/kg n= 369 and Ipilimumab 10 mg/kg and n = 366

Events/number of subjects, n/N (%)	**93/369 (25.2%)**	**115/366 (31.4%)**
Median DMFS (95% CI)[a], months	**N.A.**	**N.A.**
HR (95% CI)[b]	**0.73 (0.55, 0.95)**	
Stratified log rank p-value[e]	**0.0204**	
Rate at 12 months, % (95% CI)[a]	**80.2 (75.6, 83.9)**	**73.4 (68.4, 77.7)**
Rate at 18 months, % (95% CI)[a]	**75.1 (70.3, 79.3)**	**66.6 (61.2, 71.3)**

At the time of the database lock, 276/369 (74.8%) subjects in the nivolumab group and 251/366 (68.6%) subjects in the ipilimumab group were censored for DMFS.

Among those censored, most were in follow-up; 264 (71.5%) in the nivolumab group and 234 (63.9%) in the ipilimumab group.

Health-related quality of life-secondary endpoint: EORTC general cancer module (QLC-C30)

The EORTC QLQ-C30 is the most commonly used quality-of-life instrument in oncology trials. Raw scores for the EORTC QLQ-C30 are transformed to a 0-100 metric such that higher scores for all functional scales and Global Health Status indicate better HRQoL Lower scores for symptom scales indicate better HRQoL. A difference of 10 points on a 100 point scale between the two treatment arms is considered clinically significant.

Questionnaire completion rates at baseline were 97.8% (443/453) in the nivolumab group and 96.0% (435/453) in the ipilimumab group, 86% and 84% respectively through 49 weeks, and 76% and 71% at follow-up, respectively. While some of the functional and symptom scores worsened over time in both groups, the CSR states no mean change score from baseline reached the minimal important difference for the patient (that is, mean change ≥10 points) at any time point for either treatment group, overall or for individual functioning or symptom scales.

Comment: Diarrhoea symptom score recorded for ipilimumab group at the first follow-up time point had a mean change from baseline score of 11.08 versus 0.62 for nivolumab, but this was not reflected at other time points.

The sponsor's Clinical Overview included the following additional information:

> *Recognizing that the standard of care in the EU is frequently observation, an overlay of QoL curves for nivolumab in CA209238 versus placebo in CA184029 was generated. Despite the differences in baseline characteristics of the populations and study designs, QoL results (assessed using the EORTC QLQ-C30 Global Health score) were comparable between nivolumab in CA209238 and placebo in CA184029, with small variations in the mean change scores from baseline that did not reach the minimal important difference for the patient (±10 points from baseline).*

Patient-reported general health status–exploratory endpoint: Patient-reported general health status (EQ-5D-3L5)

EQ-5D-3L5 is a generic multi-attribute health-state classification system by which health is described in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses on 3 levels (no, some or severe problems) are converted into unique EQ-5D health state descriptions and a representative utility. A VAS self-rating is also included. A mean change score from baseline of 0.08 for the EQ 5D utility score and of 7 for the EQ 5D VAS were considered as the minimal important difference (MID) estimates for the EQ 5D. At baseline, mean EQ-5D utility index scores and EQ-5D VAS for 'All Randomized subjects' were comparable between treatment groups.

The CSR states that no mean change score from baseline reached the MID for the patient at any time point for either treatment group.

Comment: Overall, fewer than 5% of patients in either group self-reported severe problems.

Work Productivity Activity Impairment-exploratory endpoint: WPAI:GH

The WPAI:GH is a six-item questionnaire yielding four different scale scores. It was created as a patient-reported quantitative assessment of the amount of absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness), work productivity (overall work impairment/absenteeism plus presenteeism) and daily activity impairment attributable to general health. An MID has not been established for the WPAI:GH in melanoma. One-half the standard deviation (SD) of scores at baseline was used as an estimate of MID for each of the WPAI:GH scales. Completion rates in both groups were similar to the other health-related questionnaires.

- At baseline, mean WPAI:GH summary scale scores for 'All Randomized subjects' were comparable between treatment groups, and no clinically meaningful deterioration or improvement was observed at any time point for either treatment group for any scale.

7.2.1.14. Evaluator commentary

In Study CA209238 OS was specified as a secondary variable but has not yet been reported. Benefit on RFS as a predictor of benefit on OS requires longer follow-up.

Post-recurrence treatment across the two arms of the trial is likely to be a confounder for assessment of OS. Meta-analyses of previous adjuvant treatment data support the choice of RFS as the primary variable as surrogate for OS in adjuvant melanoma.

Stratification by disease stage and PD-L1 expression would be expected to contribute to minimisation of bias.

Toxicity profiles for ipilimumab and nivolumab are well known and differences across the treatment arms may compromise blinding.

Imbalance across treatment arms of potentially prognostic/predictive factors could introduce bias and reduce internal validity. In Study CA209238, differences for each characteristic were small.

The Kaplan-Meier curves for RFS in Study CA209238 separated early, with a sustained separation.

Overall the primary efficacy analysis showed a significant improvement in RFS in the population with completely resected 'No evidence of disease' Stage IIIB/C or Stage IV melanoma for adjuvant treatment with nivolumab compared to ipilimumab.

The estimated one year RFS rates (95% CI) from Kaplan-Meier curves were:

- Nivolumab 70.5% (66.1, 74.5) versus ipilimumab 60.8% (61.8, 70.6).

Baseline PD-L1 expression was associated with a lower risk of recurrence for nivolumab. Nivolumab showed benefit compared to ipilimumab for RFS regardless of PD-L1 expression status, as defined by the 5% cut-off in this study.

The requested indication includes all Stage III melanoma, not just the Stage IIIB/C population included in Study CA209238.

The sponsor provided justification for this extrapolation in their Clinical Overview, stating that as consistent benefit was seen across Stage IIIB/C and Stage IV in Study CA209238, and the stages represent the same pathologic mechanism along a continuum, then a similar treatment benefit would be expected in subjects with resected Stage IIIA melanoma.

However the evaluator notes that for patients with a lower risk of recurrence, the risk/benefit consideration might place greater weight on safety aspects.

7.3. Other efficacy studies

A supportive study was provided detailing efficacy and safety data in patients with resected Stage III melanoma for ipilimumab, the active comparator in Study CA209238. Ipilimumab ('Yervoy') is a CTLA-4 monoclonal antibody approved in Australia for the treatment of unresectable or metastatic melanoma at a dose of 3mg/kg.

While this study was not directly relevant to the indications sought for nivolumab, the information is relevant to the validity of ipilimumab as the active comparator in Study CA209238, and also provided information about this patient group when receiving no active treatment, that is, the placebo arm. An abbreviated description follows.

7.3.1. Study CA184029 (also known as EORTC 18071)

7.3.1.1. Study design and duration

This was a double-blind randomised parallel two–arm Phase III study of ipilimumab 10 mg/kg versus placebo in patients with resected Stage III melanoma, to determine whether post-operative adjuvant therapy with ipilimumab improves RFS, OS, and DMFS, and evaluate AE profiles and QoL, compared to placebo.

The patient population had complete resection of Stage IIIA (> 1mm metastasis), IIIB, and IIIC (no in-transit metastases) cutaneous melanoma and were randomised 1:1 to receive ipilimumab 10 mg/kg or placebo during induction (dosing every 3 weeks for 4 doses) and maintenance (dosing at 12 week intervals) from Week 24 up to a maximum of 3 years from randomisation, or until recurrence, unacceptable toxicity, or subject withdrawal.

Subjects were screened for eligibility and then randomised, no longer than 12 weeks from the last surgery for complete and adequate resection of Stage III melanoma that made the subject free of disease.

Treatment started within 7 days from randomisation, after full wound healing. Follow-up phase began with disease recurrence event, treatment for 3 years, or withdrawal of consent from study procedures. Treatment during follow-up was left to investigator discretion, but cross-over to ipilimumab was not allowed.

Placebo was chosen as a comparator because of lack of evidence of clear clinical benefit, especially for survival, for existing adjuvant treatment for this patient population.

Disease was assessed at baseline and every 12 weeks for 3 years, then every 24 weeks until distant progression. Toxicity was assessed every 3 weeks (induction) then every 12 weeks (maintenance).

7.3.1.2. Analysis Populations and statistical analyses

ITT was all randomised subjects, and used for baseline demography, patient characteristics, and main efficacy analyses. The criteria for relevant protocol deviations were listed and stated to have been discussed and aligned by sponsor and EORTC medical monitors. A Per Protocol population was used to perform sensitivity analyses for efficacy.

Time-to-event variables were compared using a log-rank test and summarised using Kaplan-Meier plots. There was a hierarchy of testing for RFS, OS, and DMFS. The CSR provided with this submission contained the final RFS analysis.

The HR and its 95% confidence interval of ipilimumab to placebo were estimated using a Cox proportional hazards model, stratified by disease stage (IIIA versus IIIB versus IIIC with 1-3 positive lymph-nodes versus IIIC with ≥ 4 positive lymph-nodes) as indicated at randomisation, with treatment as the single covariate.

7.3.1.3. Efficacy endpoints

Recurrence-free survival

The primary endpoint of RFS per IRC was programmatically determined based on the disease recurrence data provided by the IRC and was defined as the time between the date of randomisation and date of first recurrence (local, regional or distant metastasis) or death (whatever the cause), whichever occurs first.

All radiologic imaging from this trial were reviewed in a blinded and sequential fashion by an IRC to uniformly assess recurrence.

Yearly recurrence-free survival rates, for example, at 1 year, defined as the probability that a subject was recurrence-free at 1 year following randomisation, were estimated for each

treatment group using the Kaplan-Meier product-limit method, along with their corresponding log-log transformed 95% confidence intervals.

Recurrence free survival per investigator was also analysed using the Kaplan-Meier method.

Overall survival

Secondary efficacy analyses for OS and DMFS were not included in the initial CSR but were provided in Addendum 02 following database lock on 13 May 2016.

7.3.1.4. Participant flow

Of 1211 subjects enrolled and screened for study participation, a total of 951 (78.5%) were randomised, 475 to ipilimumab and 476 to placebo.

In the ipilimumab group, the most common reason for discontinuation of study drug was due to an AE (51.8%) followed by recurrence of disease (28.0%). In the placebo group, the most common reason for discontinuation of study drug was recurrence of disease (57.6%) followed by normal completion (13.3%). In the ipilimumab group 5.1% completed treatment versus 13.3% placebo. In the ipilimumab group 164 subjects (34.8%) received subsequent antitumor therapy compared with the placebo group 218 subjects (46.0%).

7.3.1.5. Protocol deviations

Significant protocol deviations were defined as those that could have had an impact on the primary results of the study, those of ethical concern, and those which could have posed a safety risk to the subject. As deviations were identified, sites were re-trained to prevent or avoid future occurrences.

Relevant protocol deviations are those protocol deviations that could have had a major impact on the interpretability of the main results of the study, and were predefined. Fewer subjects had relevant eligibility deviations in the ipilimumab group, 13 (2.7%) than in the placebo group, 21(4.4%); corresponding on-study relevant protocol deviations were 4.2% versus 3.4%. Collectively these were assessed as not affecting the interpretability of results.

7.3.1.6. Baseline data

Demographic characteristics were generally comparable between the ipilimumab and placebo treatment groups. Median age was 51.0 years; 167 (17.6%) subjects were ≥ 65 years of age and 21 (2.2%) subjects were ≥ 75 years of age. The majority were White (946/951, 99.5%) and had ECOG performance status 0 (893/951, 93.9%).

Baseline disease characteristics were balanced between the ipilimumab and placebo treatment groups. About 20% had Stage IIIA at study entry, 44 % Stage IIIB, 16% Stage IIIC with 1-3 positive lymph nodes, 20% Stage IIIC with ≥ 4 positive lymph nodes.

7.3.1.7. Primary efficacy endpoints

RFS

There was a statistically significant improvement of RFS as assessed by IRC in subjects randomised to ipilimumab 10 mg/kg compared to placebo. With a median follow-up of 2.7 years, a total of 528 (55.5%) subjects (234/475, 49% ipilimumab and 294/476, 62% placebo) had recurrence (that is, local, regional or distant metastasis as provided by the IRC or death).

HR for comparison of RFS (per IRC) between the groups was 0.75 (95% CI: 0.64, 0.90; p = 0.0013). For the PP analysis the HR was 0.77(0.65, 0.92); p=0.0033.

The median time to RFS (per IRC) was 26.1 months (95% CI: 19.3, 39.3) for ipilimumab and 17.1 months (95% CI: 13.4, 21.6) for placebo. Recurrence -free survival rates were presented based on Kaplan-Meier estimations:

Table 18: Kaplan-Meier estimations

	10 mg/kg Ipilimumab (N=475)	Placebo (N=476)
RFS Rate at 1 Year (%) 95% CI	63.50 (58.89, 67.74)	56.13 (51.52, 60.47)
RFS Rate at 2 Years (%) 95% CI	51.45 (46.69, 56.00)	43.83 (39.27, 48.28)
RFS Rate at 3 Years (%) 95% CI	46.48 (41.46, 51.34)	34.79 (30.12, 39.50)

While there were some discrepancies between IRC and investigator assessments, the Kaplan-Meier curves were similar. The HR per investigator was 0.73 (95% C I 0.62, 0.87; p=0.0005).

Overall Survival

This endpoint was reported in Addendum 2 to the CSR, together with DMFS.

The Kaplan-Meier curves for OS and DMFS (per IRC) for ipilimumab and placebo separated after approximately 3 months, favouring ipilimumab through 4+ years.

The 5 year OS rates were not considered mature at the time the Addendum report was written, as the potential minimum follow-up across all subjects was 53 months (that is, approximately 4.5 years).

Table 19: Overall survival rates Intent-to-Treat (ITT) population

	Number of Subjects	
	10 mg/kg Ipilimumab (N=475)	Placebo (N=476)
OS Rate at 1 Year (%) 95% CI	93.53 (90.88, 95.43)	87.72 (84.40, 90.37)
OS Rate at 2 Years (%) 95% CI	82.55 (78.76, 85.73)	75.27 (71.10, 78.92)
OS Rate at 3 Years (%) 95% CI	74.20 (69.90, 77.98)	65.43 (60.91, 69.56)
OS Rate at 4 Years (%) 95% CI	67.79 (63.24, 71.90)	60.34 (55.72, 64.64)
OS Rate at 5 Years (%) 95% CI	65.42 (60.80, 69.64)	54.43 (49.71, 58.89)

Based on Kaplan-Meier estimation and confidence intervals (CI) computed using log-log transformation.
Analysis of OS rate at 5 years conducted post 2Q2016 will be considered mature.

For OS, the 4-year rates (95% CI) in the ipilimumab and placebo groups were 67.8% (63.24, 71.90) and 60.3% (55.72, 64.64), respectively.

The corresponding rates were 50.2% (45.30, 54.87) and 41.48% (36.87, 46.02), respectively, for DMFS (per IRC).

Of note, for Stage IIIA 24/98 subjects died in the ipilimumab groups versus 22/88 in the placebo group, HR 0.98 (95% CI 0.55-1.74).

7.3.2. Evaluator commentary on other efficacy studies

For comparison with Study CA209238, the median time to RFS (per IRC) was 26.1 months (95% CI: 19.3, 39.3) for ipilimumab and 17.1 months (95% CI: 13.4, 21.6) for placebo.

The recurrence-free survival rates at 1 year were 63.5% for ipilimumab and 56.1% for placebo. This can be considered for perspective on the 1 year RFS rates reported in Study CA209238; 70.5 % for nivolumab, and 60.8% for ipilimumab.

Overall survival at 1 year was around 90% ipilimumab versus 87% for the placebo group, and at 4 years OS was 68% for ipilimumab versus about 60% for placebo. The 5 year OS rates were not considered mature at the time of the report provided; 65% versus 54%.

7.4. Analyses performed across trials: pooled and meta analyses

There were no meta-analyses related to this submission for nivolumab in adjuvant melanoma indication.

7.5. Evaluator's conclusions on clinical efficacy

In the interim CSR for Study CA209238 the primary efficacy analysis showed a significant improvement in RFS in the population with completely resected Stage IIIB/C or Stage IV melanoma, for adjuvant treatment with nivolumab compared to ipilimumab.

The 1 year RFS rates (95% CI) estimated from Kaplan-Meier curves were nivolumab 70.5% (66.1, 74.5) versus ipilimumab 60.8% (61.8, 70.6).

Pre-specified analyses of multiple sub-groups were supportive of the overall findings.

The evaluator remains uncertain about the implications of the 5% cut-off for positive/negative PD-L1 expression status.

The RFS rate for ipilimumab in Study CA209238 was consistent with the findings in Study CA184029 (also known as EORTC 18071) trial, that is, RFS at 1 year in Study CA184029 was 63.5% with the same dose of ipilimumab. This provides some indirect support for validity of the Study CA209238 findings, although the patient groups were not exactly the same; the pivotal Study CA209238 for this submission included Stage IV resected melanoma and excluded Stage IIIA resected melanoma, whereas Study CA184029 excluded Stage IV and about 20% of subjects had resected Stage IIIA melanoma.

For context, reflecting 'observation', the RFS rate in supportive Study CA184029 for the placebo arm at one year was 56%, and 44% and 35% at 2 and 3 years respectively. While these represent cross-study comparisons, an improvement in RFS of more than 10% might be expected for nivolumab adjuvant treatment compared to 'observation' over 1 year. Also for context, it is noted that OS for the placebo arm of Study CA184029 was 60% at 4 years.

8. Clinical safety

Clinical safety was addressed in the efficacy/safety studies provided. Safety data were available from the interim CSR for Study CA209238 for nivolumab in adjuvant melanoma treatment.

Apart from the CSR, additional safety analyses were prepared for the sponsor's Summary of Clinical Safety (SCS). These SCS analyses used a safety window of 30 days and 100 days (that is, extended follow-up) after last dose and included summaries of:

- On-treatment worst CTC grade laboratory parameters that worsened relative to baseline (SI units)
- All Grade 3-4 AEs
- Any AEs leading to discontinuation, SAEs, and any Grade 3-4 AEs excluding terms clearly not study drug related
- All causality and drug-related AEs (remapped terms) to support the product information, including terms included and excluded from product information
- Individual standardized MedDRA query (SMQ) broad and narrow scopes.

The SCS included support for the proposed wording for 'Adverse reactions' in the SmPC.

The SCS also provided comparison with updated pooled safety data for nivolumab in other tumour indications.

The currently approved Australian PI contains pooled safety data assessed to date for nivolumab.

8.1. Studies providing evaluable safety data

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.1.2. Study CA209238

Safety was assessed as described below and the sponsor concluded that no new safety concerns were identified for nivolumab or ipilimumab monotherapy.

8.1.3. Other studies

8.1.3.1. Study CA184209

Safety of ipilimumab 10 mg/kg every three weeks for 4 doses (induction) then at 12 week intervals from week 24 (maintenance) for maximum 3 years, was assessed in comparison to placebo as adjuvant melanoma treatment in subjects with completely resected Stage IIA/B/C cutaneous melanoma.

The safety data from this study were reviewed and brief summary information from the study is included in this CER, to provide context for the safety profiles for both the comparator ipilimumab and placebo treatments for resected melanoma.

8.2. Studies that assessed safety as the sole primary outcome

Not applicable.

8.3. Patient exposure

Exposure to nivolumab and ipilimumab in Study CA209238 is summarised in Table 20 below.

Table 20: Exposure to nivolumab and ipilimumab in Study CA209238

Study type/ Indication	Controlled studies			Uncontrolled studies	Total Nivolumab
	Nivolumab	Placebo	Ipilimumab	Nivolumab	
Study CA209238 for adjuvant melanoma Cumulative dose(mg/kg)	N = 452 Mean 58.90 (SD 23.827) Median 72 Range 3-80.1	n/a	N = 453 Mean 41.07(SD 18.340) Median 40 Range 9.8-70	n/a	N = 453

* Control = Comparator

In Study CA209238 the median number of doses received was 24 for nivolumab group (range 1-26) versus 4 for ipilimumab (range 1-7). The proportion of treated subjects who received ≥ 90% of the planned dose intensity was 86.3% in the nivolumab group and 80.1% in the ipilimumab group.

See Tables 21 and 22 for Doses received and Dose omissions/interruptions below.

Table 21: Study CA209238 Doses received

	Nivolumab 3 mg/kg N = 452		Ipilimumab 10 mg/kg N = 453	
	Nivolumab	Ipilimumab Placebo	Nivolumab Placebo	Ipilimumab
NUMBER OF DOSES RECEIVED				
MEAN (SD)	19.6 (7.94)	5.8 (1.50)	11.2 (9.05)	4.1 (1.84)
MEDIAN (MIN - MAX)	24.0 (1 - 26)	7.0 (1 - 7)	6.0 (1 - 26)	4.0 (1 - 7)
NUMBER OF DOSES RECEIVED				
1	4 (0.9)	6 (1.3)	6 (1.3)	19 (4.2)
2	4 (0.9)	8 (1.8)	45 (9.9)	89 (19.6)
3	6 (1.3)	19 (4.2)	57 (12.6)	79 (17.4)
4	6 (1.3)	81 (17.9)	49 (10.8)	104 (23.0)
5	10 (2.2)	37 (8.2)	38 (8.4)	35 (7.7)
6	14 (3.1)	73 (16.1)	41 (9.1)	51 (11.3)
7	17 (3.8)	228 (50.4)	16 (3.5)	76 (16.8)
> 7	388 (85.8)	0	201 (44.4)	0
CUMULATIVE DOSE (MG/KG)				
MEAN (SD)	58.90 (23.827)	N.A.	N.A.	41.07 (18.340)
MEDIAN (MIN - MAX)	72.00 (3.0 - 80.1)	N.A.	N.A.	40.00 (9.8 - 70.0)
RELATIVE DOSE INTENSITY				
>= 110%	0	N.A.	N.A.	0
90% TO < 110%	390 (86.3)	N.A.	N.A.	363 (80.1)
70% TO < 90%	59 (13.1)	N.A.	N.A.	72 (15.9)
50% TO < 70%	3 (0.7)	N.A.	N.A.	17 (3.8)
< 50%	0	N.A.	N.A.	1 (0.2)

Table 22: Dose omission/interruption

	Nivolumab 3 mg/kg N = 452	Ipilimumab 10 mg/kg N = 453
DOSE OMISSION		
SUBJECTS WITH AT LEAST ONE OMITTED DOSE (%)	160 (35.4)	89 (19.6)
NUMBER OF OMITTED DOSES PER SUBJECT (%)		
0	292 (64.6)	364 (80.4)
1	77 (17.0)	73 (16.1)
2	36 (8.0)	13 (2.9)
3	30 (6.6)	3 (0.7)
>= 4	17 (3.8)	0
TOTAL NUMBER OF OMITTED DOSES	325	108
REASON FOR OMITTED DOSE (A)		
ADVERSE EVENT	196 (60.0)	77 (71.3)
OTHER	108 (33.2)	24 (22.2)
NOT REPORTED	22 (6.8)	7 (6.5)
DOSE INTERRUPTION		
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	11 (2.4)	18 (4.0)
NUMBER OF INFUSIONS INTERRUPTED PER SUBJECT (%)		
0	441 (97.6)	435 (96.0)
1	8 (1.8)	17 (3.8)
2	2 (0.4)	0
3	0	1 (0.2)
>= 4	1 (0.2)	0
TOTAL NUMBER INFUSIONS INTERRUPTED/TOTAL NUMBER OF INFUSIONS RECEIVED	17/8873 (0.2)	20/1863 (1.1)
REASON FOR INFUSION INTERRUPTION (B)		
HYPERSENSITIVITY REACTION	6 (35.3)	10 (50.0)
INFUSION ADMIN ISSUES	3 (17.6)	3 (15.0)
OTHER	8 (47.1)	7 (35.0)

Median duration of therapy (Kaplan-Meier estimation) (95% CI) was 11.5 months (11.47, 11.53) for nivolumab and 2.73 months (2.33, 3.25) for ipilimumab.

From the answer to Clinical Question 4, the *minimum follow-up* for subjects in Study CA209238 was 17.5 months.

Table 23: Exposure to nivolumab in Study CA209238 according to dose and duration

Study type/ Indication	Proposed dose range			
	> 6 months	>9 months	> 12 months	Any duration
Indication: adjuvant melanoma				Mean no. of doses 19.6 (SD 7.94)

Study type/ Indication	Proposed dose range			
	> 6 months	>9 months	> 12 months	Any duration
3 mg/kg				
Active controlled	N = 336	N = 298	N= 1	N = 452

8.4. Adverse events

For Study CA209238 adverse events were reported during treatment, at 30 days after last study drug treatment, and also at 100 days after last study treatments. Specifically noted were immune-mediated AEs (IMAEs)/ Immune-related AEs (IRAEs), the incidence of immunogenicity, and other events of special interest previously described for nivolumab in other indications.

For Study CA184029 analyses of safety were for data obtained from start of blinded study drug dosing up to 70 days after the last dose of study drug (on-study). Immune-related adverse events (irAEs) were programmatically determined from a pre-defined list of Medical Dictionary for Regulatory Activities (MedDRA) terms representing AEs potentially associated with inflammation and considered by the investigator to be causally related to study drug based on program-wide experience with ipilimumab.

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

8.4.1.1. Integrated safety analyses

As there was only one study of nivolumab for adjuvant melanoma treatment, the sponsor's Summary of Clinical Safety related mainly to the safety data as reported for the interim CSR for Study CA209238.

To support the proposed SmPC wording, the sponsor generated summary tables of clinically relevant adverse reactions, with some MedDRA PTs 'remapped' or 'deleted'. Some PTs that represented the same or similar clinical conditions were pooled. Some drug-related AEs that were overly general/nonspecific, had no suspected causal relationship to nivolumab per BMS medical review, were single case events with limited data, or a medical concept captured under a different term, were deleted in this 'remapping' process.

The 'remapped' adverse reactions that were considered by the BMS reviewer to be clinically relevant were presented as a large table, showing selected ADRs reported for nivolumab in adjuvant melanoma treatment compared with corresponding frequencies for pooled monotherapy treatment with nivolumab for other indications.

See Table 24 for the most common adverse events and reactions, comparing nivolumab for adjuvant melanoma with a pooled nivolumab monotherapy population in other tumour indications.

Table 24: Adverse events and reactions with nivolumab monotherapy in clinical trials using re-mapped terms

	CA209238		Monotherapy Pooled	
	Nivolumab 3mg/kg N = 452		Nivolumab 3mg/kg N = 2950	
Preferred Term (%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
TOTAL SUBJECTS WITH AN EVENT (REGARDLESS OF CAUSALITY)	438 (96.9)	115 (25.4)	2868 (97.2)	1348 (45.7)
Most Frequent (>20% in any grade in Study CA209238 or the pool across tumor types)				
FATIGUE	259 (57.3)	4 (0.9)	1361 (46.1)	127 (4.3)
MUSCULOSKELETAL PAIN	143 (31.6)	2 (0.4)	946 (32.1)	88 (3.0)
NAUSEA	104 (23.0)	1 (0.2)	725 (24.6)	22 (0.7)
COUGH	88 (19.5)	0	716 (24.3)	8 (0.3)
DIARRHOEA	167 (36.9)	11 (2.4)	681 (23.1)	57 (1.9)
RASH	157 (34.7)	5 (1.1)	654 (22.2)	34 (1.2)
DECREASED APPETITE	38 (8.4)	0	611 (20.7)	37 (1.3)
PRURITUS	127 (28.1)	0	523 (17.7)	4 (0.1)
HEADACHE	106 (23.5)	2 (0.4)	360 (12.2)	11 (0.4)
ABDOMINAL PAIN	94 (20.8)	1 (0.2)	488 (16.5)	52 (1.8)
TOTAL SUBJECTS WITH AN EVENT (DRUG-RELATED)	385 (85.2)	65 (14.4)	2063 (69.9)	454 (15.4)
Most Frequent (>10% in any grade in Study CA209238 or the pool across tumor types)				
FATIGUE	210 (46.5)	3 (0.7)	818 (27.7)	50 (1.7)
RASH	129 (28.5)	5 (1.1)	474 (16.1)	29 (1.0)
PRURITUS	105 (23.2)	0	383 (13.0)	3 (0.1)
DIARRHOEA	110 (24.3)	7 (1.5)	358 (12.1)	32 (1.1)
NAUSEA	68 (15.0)	1 (0.2)	325 (11.0)	5 (0.2)
ARTHRALGIA	57 (12.6)	1 (0.2)	167 (5.7)	2 (<0.1)
MUSCULOSKELETAL PAIN	51 (11.3)	2 (0.4)	202 (6.8)	10 (0.3)
HYPOTHYROIDISM	50 (11.1)	1 (0.2)	183 (6.2)	3 (0.1)

MedDRA Version: 20.0, CTC Version 4.0.
Includes events reported between first dose and 30 days after last dose of study therapy, except for GND-4538-12.
For GND-4538-12 includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Some preferred terms are re-mapped or deleted based on BMS medical review.
Monotherapy Pooled group consists of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205, CA209141, CA209275, GND-4538-12 and CA209032 (UC and GC/GEJ 3L+ subjects)

Comment: The current Australian PI for nivolumab refers to 'adverse reactions', as does the SmPC, so the drug-related event frequencies are the most relevant information. See 8.4.2 for further details of the comparison.

The Australian PI shows currently approved pooled nivolumab safety information.

8.4.1.2. Study CA209238

Any grade AEs occurred in 438 (96.9%) nivolumab subjects and 446 (98.5%) ipilimumab subjects. Grade 3/4 AEs were 115 (25.4%) and 250 (55.2%) respectively.

For nivolumab the most frequently reported AEs were fatigue (42.7%), diarrhoea (36.9%), pruritus (28.1%), rash (25.4%), headache (23.5%), and nausea (23.0%).

In the ipilimumab group, the most frequently reported AEs were diarrhoea (54.5%), fatigue (40.8%), pruritus (36.9%), rash (33.1%), headache (31.3%), nausea (28.0%), and pyrexia (21.2%).

Grade 3/4 AEs (regardless of causality) were reported in 25.4% of subjects in the nivolumab group and 55.2% of subjects in the ipilimumab group. For nivolumab the most frequently reported Grade 3/4 AEs were lipase increased (4.9%), diarrhoea (2.4%), and amylase increased (2.4%). For ipilimumab the most frequently reported Grade 3/4 AEs were diarrhoea (10.6%), colitis (7.7%), and alanine aminotransferase (ALT) increased (6.2%).

8.4.1.3. Other studies-CA184029

AEs were more frequently reported in the ipilimumab group than the placebo group. Any on-study AEs were reported by 465/471(98.7%) of ipilimumab subjects versus 432/474 (91.1%) of subjects receiving placebo. For grade 3-4 events the corresponding frequencies were 254 (53.9%) versus 118 (24.9%).

For ipilimumab 10 mg/kg in adjuvant melanoma, similar types of AEs were observed but at a higher frequency than in previous Phase II and III studies of 10 mg/kg ipilimumab in advanced melanoma. Very common AEs regardless of causality included: diarrhoea 49% ipilimumab versus 30% placebo, nausea 25% versus 17%, abdominal pain 14% versus 9%, vomiting 13%

versus 6%, colitis 16% versus 1%, pruritus 43% versus 15%, rash 40% versus 17%, weight decreased 31% versus 8%, fatigue 40% versus 30%, and hypophysitis 18% versus 0.6%.

8.4.2. Treatment related adverse events (adverse drug reactions)

'Drug-related adverse events' are taken to be the source of 'Adverse drug reactions' provided in the proposed PI, as for the SmPC.

As noted above, AE reports from the CSR for Study CA209238 were 're-mapped' by the BMS medical reviewer to *pool* PTs representing the same or similar clinical conditions, *delete* some overly general/nonspecific PTs, and to comply with the EMA definitions for ADRs (causal relationship at least a reasonable possibility) and requirements for the SmPC.

Comment: The current Australian PI for nivolumab refers to 'adverse reactions' and does not give full details of AEs reported for the clinical studies supporting each indication, but provides pooled safety data. This is in line with the format and content of the EMA-approved SmPC at the EMA.europa.eu website.

In contrast, the USPI includes summaries of safety for studies supporting each indication; see the relevant pages on the accessdata.fda.gov website for Opdivo.

The 'Adverse Reactions' described in the US PI, updated with the adjuvant treatment of melanoma, reflect all-causality AEs occurring in ≥ 20%, as for the 're-mapped 'events provided for this submission; see also Table 25 for the most frequent AEs/ADRs nivolumab monotherapy Study CA209238 versus pooled, using re-mapped terms below.

Additional terms included in the USPI occurred at ≥10%.

Table 25: Most frequent AEs/ADRs nivolumab monotherapy Study CA209238 versus pooled using re-mapped terms

	CA209238		Monotherapy Pooled	
	Nivolumab 3mg/kg N = 452		Nivolumab 3mg/kg N = 2950	
Preferred Term (%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
TOTAL SUBJECTS WITH AN EVENT (REGARDLESS OF CAUSALITY)	438 (96.9)	115 (25.4)	2868 (97.2)	1348 (45.7)
Most Frequent (>20% in any grade in Study CA209238 or the pool across tumor types)				
FATIGUE	259 (57.3)	4 (0.9)	1361 (46.1)	127 (4.3)
MUSCULOSKELETAL PAIN	143 (31.6)	2 (0.4)	946 (32.1)	88 (3.0)
NAUSEA	104 (23.0)	1 (0.2)	725 (24.6)	22 (0.7)
COUGH	88 (19.5)	0	716 (24.3)	8 (0.3)
DIARRHOEA	167 (36.9)	11 (2.4)	681 (23.1)	57 (1.9)
RASH	157 (34.7)	5 (1.1)	654 (22.2)	34 (1.2)
DECREASED APPETITE	38 (8.4)	0	611 (20.7)	37 (1.3)
PRURITUS	127 (28.1)	0	523 (17.7)	4 (0.1)
HEADACHE	106 (23.5)	2 (0.4)	360 (12.2)	11 (0.4)
ABDOMINAL PAIN	94 (20.8)	1 (0.2)	488 (16.5)	52 (1.8)
TOTAL SUBJECTS WITH AN EVENT (DRUG-RELATED)	385 (85.2)	65 (14.4)	2063 (69.9)	454 (15.4)
Most Frequent (>10% in any grade in Study CA209238 or the pool across tumor types)				
FATIGUE	210 (46.5)	3 (0.7)	818 (27.7)	50 (1.7)
RASH	129 (28.5)	5 (1.1)	474 (16.1)	29 (1.0)
PRURITUS	105 (23.2)	0	383 (13.0)	3 (0.1)
DIARRHOEA	110 (24.3)	7 (1.5)	358 (12.1)	32 (1.1)
NAUSEA	68 (15.0)	1 (0.2)	325 (11.0)	5 (0.2)
ARTHRALGIA	57 (12.6)	1 (0.2)	167 (5.7)	2 (<0.1)
MUSCULOSKELETAL PAIN	51 (11.3)	2 (0.4)	202 (6.8)	10 (0.3)
HYPOTHYROIDISM	50 (11.1)	1 (0.2)	183 (6.2)	3 (0.1)

MedDRA Version: 20.0, CTC Version 4.0.
Includes events reported between first dose and 30 days after last dose of study therapy, except for ONO-4538-12.
For ONO-4538-12 includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Some preferred terms are re-mapped or deleted based on BMS medical review.
Monotherapy Pooled group consists of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205, CA209141, CA209275, ONO-4538-12 and CA209032 (UC and GI/GEJ 3L+ subjects)

8.4.2.1. Integrated safety analyses

The sponsor's Summary of Clinical Safety includes a large frequency table displaying the 'Re-mapped' Adverse Reactions that were considered clinically relevant by the medical reviewer for

nivolumab monotherapy in Study CA209238, compared with updated pooled nivolumab monotherapy in other tumour types.

From this table, common ADRs with frequencies ≥ 1% in an updated pooled nivolumab population, n = 2950 treated subjects, included:

- URTI (1.2%)
- neutropaenia (11.7%)
- infusion-related reaction 2.9%; hypersensitivity 1.4%
- hypothyroidism 6.2%; hyperthyroidism 2.2%
- decreased appetite 8.6%
- peripheral neuropathy 2.1%; headache 3.5%; dizziness 1.8%
- hypertension 1.1%
- pneumonitis 3.2%; dyspnoea 4.5%; cough 4.3%
- diarrhoea 12.1%, nausea 11.0%; colitis 1.2%; stomatitis 2.8%; vomiting 4.9%; abdominal pain 3.5%; constipation 4.1%; dry mouth 2.5%
- rash 16.2%; pruritus 13.0%; vitiligo 2.7%; dry skin 3.5%; erythema 1.5%; alopecia 1.1%
- musculoskeletal pain 6.8%; arthralgia 5.7%
- fatigue 27.7%; pyrexia 5.6%; oedema 2.9%

Judging by this comparison table, the pattern of ADRs was similar in the adjuvant melanoma Study CA209238; see Section 8.4.2.2.

However some ADR frequencies in the adjuvant melanoma 'AM' database from Study CA209238 were notably higher than for the pooled nivolumab frequencies provided in this table. For nivolumab in adjuvant melanoma (Study CA209238) versus nivolumab in pooled population treated for other tumours these included:

- hypothyroidism 11.1% versus 6.2%; hyperthyroidism 8.4% versus 2.2%; hypophysitis 1.5% versus 0.3%; thyroiditis 2.2% versus 0.6%;
- headache 9.7% versus 3.5%; dizziness 3.5% versus 1.8%; vision blurred 1.3% versus 0.6%; dry eye 2.2% versus 0.8%;
- diarrhoea 24.3% versus 12.1%; nausea 15.0% versus 11.0%; abdominal pain 9.3% versus 3.5%; dry mouth 5.3% versus 2.5%;
- rash 28.5% versus 16.2%; pruritus 23.2% versus 13.0%; erythema 4.4% versus 1.5%;
- musculoskeletal pain 11.3% versus 6.8%; arthralgia 12.6% versus 5.7%;
- fatigue 46.5% versus 27.7 %.

Comment: The sponsor refers to these higher frequencies in Study CA209238 in the context of all-causality and drug-related comparisons stating:

> '*This may not be unexpected given the intact immune system in patients in the adjuvant setting as compared to patients with more advanced disease'* (sponsor's Summary of Clinical Safety)

See Section 8.5 below for pooled laboratory and other investigations; patterns were similar for adjuvant melanoma and other tumour types.

From the current Australian PI the pooled dataset population is n = 2227 for nivolumab monotherapy adverse reactions:

In the pooled dataset of nivolumab 3 mg/kg as monotherapy across tumour types (Melanoma: CA209066, CA209037, CA209067 (monotherapy group only), SQ NSCLC: CA209017, CA209063, NS NSCLC: CA209057, RCC: CA209025, cHL: CA209205 and CA209039 and SCCHN: CA209141), the most frequent adverse reactions (≥ 10%) were fatigue (30%), rash (17%), pruritus (12%), diarrhoea (12%) and nausea (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). [1]

Grade 3/4 lipase increased (6.5%), amylase increased (2.3%), and ALT increased (2.2%) are also reported in the PI.[1]

Comment: As noted at the beginning of Section 8, the source for the re-mapped AEs and drug-related AEs for pooled nivolumab monotherapy in other tumour types (n = 2950) is cross-referenced to another SCS, for 'GC/GEJ'. This is under evaluation.

Overall, updated categories 'very common' and 'common' reactions provided with this submission for pooled nivolumab are consistent with the current frequencies provided in the PI.

8.4.2.2. Study CA209238

For nivolumab, *any-grade* drug-related AEs were reported in 85.2% of subjects and for ipilimumab, 95.8% of subjects.

The most frequently reported drug-related AEs for nivolumab from the CSR were fatigue (34.5%), diarrhoea (24.3%), and pruritus (23.2%). 'Rash' is described in with a frequency of 19.9%, together with other common reactions such as nausea 15%, arthralgia 12.6%, myalgia 7.7%, hypothyroidism 10.8%, hyperthyroidism 8.0%, and headache 9.7%.

The sponsor's Clinical Overview cites 'fatigue' at a frequency of 46.5% and 'rash' at a frequency of 28.5%, from SCS. Appendix AM.8A-PI [not included here] provided a summary of drug-related AEs as 're-mapped' preferred terms by worst CTC grade for all treated subjects, to last dose of therapy + 30 days. Here 'rash' is shown as occurring in 129/452 subjects, that is, 28.5% of all subjects.

Other frequencies given in this table are proposed for the PI for Adverse reactions with occurrence > 10%: these include nausea 15%, arthralgia 13%, musculoskeletal pain 11%, and hypothyroidism 11%.

Comment: Combining closely similar PTs, some of which are minor subsets and were reported in only a few subjects, appears reasonable and provides more realistic frequencies for clinically relevant adverse reactions. The combination of terms for 'rash' and 'musculoskeletal pain' is described in the currently approved Australian PI, as footnotes to Table 15 'Adverse reactions in clinical trials'.

This 'Re-mapping' process affects some AE counts, and frequencies in the Appendices show' re-mapped' reaction frequencies different to those provided in the original CSR for Study CA209238; for example, 'fatigue' increased to 46.5%, apparently by combining the PT 'fatigue' with 'asthenia'.

From the CSR, reports of fatigue and asthenia combined appear to be 156 + 57 = 213/452 = 47.1% for fatigue overall, but the number of subjects with fatigue shown in Appendix AM.8A-PI is 210/452= 46.5%.

Terms for 'dermatitis' such as 'dermatitis acneiform', and 'rash' with additional descriptors such as 'rash macular' and 'rash pustular', were collapsed into the overall preferred term 'rash' to be included in product information tables. The amended 'rash' frequency is given as 129/452= 28.5%. However from the Summary of drug-related Skin AEs, this would add to 'rash' = 90, rash maculo-papular 24, rash pruritic 11 rash macular 5, rash papular 3 and rash erythematous 1, with 2 dermatitis to give a total of 136/452=30%. Alternatively, if the PTs from the Interim

CSR for Study CA209238 are considered, then 9 additional subjects with 'dermatitis acneiform' would also be included, 145/452=32%. The evaluator was not able to locate the process of derivation of the 'remapped' adverse reaction frequencies to resolve these discrepancies.

The new term 'Musculoskeletal pain' included back pain, bone pain, neck pain, pain in extremity and myalgia; myalgia alone had an original frequency of 35/452 = 7.7%, but when combined with other PTs for skeletal pain there were 51/452 subjects (11.3%) who experienced 'musculoskeletal pain'.

If the cut-off was 5% this would include drug-related events such as abdominal pain, dry mouth, transaminases increased, amylase increased, lipase increased, pyrexia, hypothyroidism and hyperthyroidism.

As these events are clinically relevant, the evaluator recommends consideration of inclusion of events with frequency≥ 5% in the table.

Of note, the subsequent table in M2.7.4, Appendix AM.8B-P [not included herehere], is a summary of drug-related AEs ('re-mapped') for extended follow-up subjects (last dose + 100 days). 'Rash' frequency in this time frame was 29.4%; pruritus 23.5%, fatigue 47.1%, diarrhoea 24.8%, nausea 15.3%, abdominal pain 15.3%, dry mouth 5.3%, transaminases increased 7.7%, lipase increased 6.9%, amylase increased 6.2%, arthralgia 12.8%, musculoskeletal pain 11.3%, hypothyroidism 11.5%, hyperthyroidism 8.4%, headache 10%.

Consideration could be given to using this latter table at Appendix AM.8B-PI as the source for adverse reactions described in the PI for the adjuvant melanoma indication.

For ipilimumab from the CSR for CA2019238 the most frequently reported drug-related AEs were diarrhoea (45.9%), pruritus (33.6%), fatigue (32.9%), rash (29.4%), and nausea (20.1%). However the 'remapped' frequencies are 44.4% for 'fatigue' and 42.8% for 'rash'.

Grade 3/4 drug-related AEs were reported in 14.4% of subjects in the nivolumab group and 45.9% of subjects in the ipilimumab group.

Grade 3/4 drug-related AEs reported in ≥1% of subjects in the nivolumab group were lipase increased (4.2%), amylase increased (2.0%), diarrhoea (1.5%), ALT increased (1.1%), and rash (1.1%). 'Re-mapped', the frequency from SCS for 'transaminases increased' is 1.3%.

For ipilimumab Grade 3/4 drug-related AEs reported (CSR) in ≥1% of subjects were diarrhoea (9.5%), colitis (7.5%), ALT increased (5.7%), AST increased (4.2%), lipase increased (3.5%), rash (3.1%), hypophysitis (2.4%), rash maculo-papular (2.0%), headache (1.5%), GGT increased (1.3%), transaminases increased (1.3%), hepatitis (1.3%), and pruritus, amylase increased, and autoimmune colitis (all 1.1%). 'Re-mapped', Grade 3/4 PT 'rash' frequency is 4.9%, and 'transaminases increased' is 7.5%.

8.4.2.3. Other studies: Study-CA184029

Drug-related on-study AEs were reported for 443(94.1%) ipilimumab subjects versus 282 (59.5%) for placebo. Corresponding frequencies for on-study Grade 3-4 drug-related AEs were 216 (45%) versus 19 (4%).

Diarrhoea, pruritus, rash, and fatigue were the most frequently reported (≥ 30% of subjects) on-study drug-related AEs in the ipilimumab group. Other very common events (any grade) were nausea, colitis, abdominal pain, pyrexia, transaminases increased, weight decreased, headache, hypophysitis, and decreased appetite.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Integrated safety analyses

The SCS referred to the data to 12 June 2017 data base lock for Study CA209238 as stated below. No new information was provided about deaths in pooled nivolumab monotherapy data for other tumour indications.

The current Australian PI includes reference to fatal cases of pneumonia, neutropenia, encephalitis, myocarditis, pneumonitis and dyspnoea, colitis, TEN, SJS, myositis, and renal failure reported from clinical studies. In addition serious immune-related adverse events are described [1].

8.4.3.2. Study CA209238

Deaths

As of 12 June 2017 data base lock, 44 subjects (9.7%) had died in the nivolumab arm and 45 (9.9%) in the ipilimumab arm. The primary reason for death was disease progression for 41 subjects in each arm.

No deaths occurred within 30 days of last dose of study drug in either treatment arm. The three subjects who died within 100 days of the last dose in the nivolumab arm all had disease progression; in the ipilimumab arm 2 subjects died within 100 days of last dose, one from disease and one for 'other' reasons.

No deaths in the nivolumab group were attributed to study drug toxicity by the investigator.

Two deaths in the ipilimumab arm were attributed to study drug toxicity by the investigator, both subjects had resected Stage IIIC melanoma: a male, age 68, died due to colitis 127 days after last dose of ipilimumab, and a female, age 63, died due to medullary aplasia 203 days after the last dose of ipilimumab.

Deaths for other reasons (not related to study drug) occurred in 3 subjects in the nivolumab arm due to cerebral haemorrhage, sepsis, and septic shock; and 2 subjects in the ipilimumab arm, due to general conditions worsening, and septic shock with multi-organ failure and pneumococcal pneumonia, respectively.

The Question related to death data was answered and confirmed the above.

No death narratives were provided for nivolumab because all occurred either after 30 days post study drug or were subsequent to other RFS events that is, disease progression.

No death narratives were provided for subjects in the ipilimumab arm in the interim CSR.

The 'Death listing for all enrolled subjects' shows that many ipilimumab subjects who died had received the drug for only a few weeks.

Serious adverse events

The overall frequencies of SAEs were lower for nivolumab (17.5% of subjects, Grade 3-4 10.6%) than for ipilimumab (40.4%, Grade 3-4 31.8%).

For nivolumab the most frequently reported were melanoma recurrent (1.8%) and cellulitis (1.5%), versus for ipilimumab diarrhoea (7.7%) and colitis (7.1%).

Table 26: Study CA209238 Drug-related SAEs by worst CTC grade reported in ≥ 0.05% of subject (All treated subjects)

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 452			Ipilimumab 10 mg/kg N = 453		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	24 (5.3)	15 (3.3)	0	141 (31.1)	111 (24.5)	0
ENDOCRINE DISORDERS	5 (1.1)	3 (0.7)	0	20 (4.4)	14 (3.1)	0
HYPOPHYSITIS	2 (0.4)	2 (0.4)	0	14 (3.1)	10 (2.2)	0
LYMPHOCYTIC HYPOPHYSITIS	0	0	0	3 (0.7)	2 (0.4)	0
GASTROINTESTINAL DISORDERS	4 (0.9)	2 (0.4)	0	71 (15.7)	57 (12.6)	0
DIARRHOEA	3 (0.7)	2 (0.4)	0	32 (7.1)	21 (4.6)	0
COLITIS	1 (0.2)	0	0	32 (7.1)	27 (6.0)	0
AUTOIMMUNE COLITIS	0	0	0	5 (1.1)	5 (1.1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (0.9)	1 (0.2)	0	6 (1.3)	4 (0.9)	0
PNEUMONITIS	3 (0.7)	0	0	5 (1.1)	4 (0.9)	0
HEPATOBILIARY DISORDERS	3 (0.7)	3 (0.7)	0	15 (3.3)	13 (2.9)	0
HEPATITIS	0	0	0	5 (1.1)	4 (0.9)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.2)	1 (0.2)	0	9 (2.0)	4 (0.9)	0
PYREXIA	0	0	0	6 (1.3)	2 (0.4)	0
INVESTIGATIONS	1 (0.2)	1 (0.2)	0	12 (2.6)	10 (2.2)	0
ALANINE AMINOTRANSFERASE INCREASED	1 (0.2)	1 (0.2)	0	4 (0.9)	3 (0.7)	0
TRANSAMINASES INCREASED	0	0	0	4 (0.9)	4 (0.9)	0

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

These consisted mainly of gastrointestinal and endocrine disorders in both treatment groups, but were less frequent for nivolumab (5.3%, Grade 3-4 3.3%) than for ipilimumab (31.1%, Grade 3/4 24.5%).

The most common PTs for drug related SAEs Grades 3/4 for nivolumab were diarrhoea and hypophysitis (both reported for 2 cases, 0.4%).

For ipilimumab the most common SAEs Grades 3/4 were colitis (n = 27, 6.0%), diarrhoea (n = 21, 4.6%) and hypophysitis (n = 10, 2.2%).

SCS Appendices gave comparable frequencies to those supplied with the CSR.

8.4.3.3. Study CA184029

Overall there were 122 deaths (25.9%) in the ipilimumab 10 mg/kg arm versus 160 (33.8%) for placebo. The primary cause of death was progression of disease in the majority 110 (23.4%) for ipilimumab and 147 (31.0%) for placebo. Five deaths were considered drug-related in the ipilimumab arm versus nil for placebo.

Serious AEs were very common in both groups, but notably more frequent in the ipilimumab arm.

Table 27: SAEs in ipilimumab and placebo groups

	ipilimumab 10 mg/kg		placebo	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any on-study SAE	254 (53.9)	176 (37.4)	119 (25.1)	65 (13.7)
Drug-related on-study SAE	216 (45.9)	147 (31.2)	10 (2.1)	5 (1.1)

For ipilimumab the most frequent SAEs overall were colitis (Any grade 11.5% Grade 3/4 6.8%), diarrhoea (Any grade 7.6%, Grade 3/4 4%) and hypophysitis (8.9%, 4%).

8.4.4. Discontinuations due to adverse events

8.4.4.1. Integrated safety analyses

No new information for pooled nivolumab AEs leading to discontinuation was provided.

In the SCS additional tabulations 'excluding terms clearly not study related' were presented for 30 days after treatment and for extended follow-up (100 days following completion of study drug treatment). These tables reported 40 subjects in total (8.8%) in the nivolumab group with AEs leading to discontinuation, up to 30 days after study drug. AEs leading to discontinuation included diarrhoea, colitis, pancreatitis, increased aminotransferases, arthralgia, arthritis, adrenal insufficiency, hyperthyroidism, thyroiditis, acute hepatitis, sarcoidosis, diabetes mellitus (DM) inadequate control, cardiovascular accident (CVA), renal impairment, pneumonitis, aseptic meningitis, and rash.

In the same classification to 100 days after the last dose of study drug, 46 nivolumab subjects discontinued due to AEs 'excluding terms clearly not study related'; additional events over the longer timeframe included gastric ulcer, hyperglycaemia, and hypokalaemia.

8.4.4.2. Study CA209238

AEs leading to discontinuation were reported in 44 (9.7%) nivolumab subjects versus 193 (42.6%) ipilimumab subjects. Grade 3-4 AEs leading to discontinuation were reported in 21 (4.6%) and 140 (30.9%) subjects in the nivolumab and ipilimumab groups, respectively.

Diarrhoea and colitis were the most frequent events leading to discontinuation up to 30 days after last dose of study therapy, with respective frequencies 1.5% and 1.1% for nivolumab (all considered drug-related) versus 10.2% and 8.2% for ipilimumab (9.9% and 8.2% considered drug-related).

Overall drug-related AEs leading to discontinuation were reported in 7.7% of subjects in the nivolumab group and 41.7% of subjects in the ipilimumab group. Grade 3-4 drug-related AEs leading to discontinuation were reported in 16 subjects (3.5%) and 136 subjects (30%) in the nivolumab and ipilimumab group, respectively.

In addition to the gastrointestinal events, subjects were discontinued for transaminases increased, endocrine disorders, hepatobiliary disorders, and pneumonitis.

8.4.4.3. Study CA184029

Discontinuations due to AEs were many times more frequent for ipilimumab than for placebo.

Table 28: Discontinuations due to AEs

	ipilimumab 10 mg/kg		placebo	
	Any grade	Grade 3-4	Any grade	Grade 3-4
On-study AE leading to discontinuation	245 (52.0)	166 (35.2)	42 (8.9)	21 (4.4)
Drug-related on-study AE leading to discontinuation	224 (47.6)	154 (32.7)	7 (1.5)	3 (0.6)

Most frequent ipilimumab-related on-study AEs resulting in discontinuation were colitis, diarrhoea and hypophysitis.

8.5. Evaluation of issues with possible regulatory impact

The SCS describes identification of AEs of special clinical interest that are potentially associated with the use of nivolumab, based on the following guiding principles:

- AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies
- AEs that may require immunosuppression (for example, corticosteroids) as part of their management
- AEs whose early recognition and management may mitigate severe toxicity

- AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization.

Taking into account the types of AEs already observed across studies of nivolumab monotherapy, endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash were considered to be select AEs. Multiple event terms that may describe each of these were grouped into endocrine, gastrointestinal (GI), hepatic, pulmonary, renal, and skin select AE categories, respectively.

Although hypersensitivity/infusion reactions did not otherwise meet criteria to be considered select AEs, these were analysed along with the select AE categories because multiple event terms may be used to describe such events and pooling of terms was necessary for full characterisation.

Other Events of Special Interest (OESIs) included the following categories: demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, pancreatitis, uveitis, myocarditis, myositis, and rhabdomyolysis. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. Analyses of OESIs also had extended follow-up (100 day window).

See Table 25 Most frequent AEs/ADRs Nivolumab monotherapy Study CA209238 vs pooled, using re-mapped terms for laboratory investigations from Study CA209238 compared to SCS pooled nivolumab data.

Frequencies for some events are also briefly presented for ipilimumab and placebo arms from Study CA184029, for comparison.

8.5.1. Liver function and liver toxicity

8.5.1.1. Integrated safety analyses

From tables provided in the SCS showing ADRs for pooled nivolumab monotherapy (n = 2950) hepatitis was uncommon (0.3%) and cholestasis was rare (< 0.1%). This is consistent with the pooled nivolumab monotherapy summary in the current PI. Nivolumab Study CA209238 data (n = 452) in the comparison table 4 showed 3 cases of hepatitis (0.7%) and no subjects with cholestasis.

Increased AST (29.7%), increased ALT (22.6%), increased alkaline phosphatase (28.2%) and increased total bilirubin (10.3%) were all very common in the pooled nivolumab monotherapy population in other tumour types from the SCS.

Corresponding frequencies for Study CA209238 were comparable for increased AST (23.6%) and ALT (25.3%), and notably lower for increased alkaline phosphatase (7.9%). Increased bilirubin frequency was 7.4%.

The SCS with preferred terms 'clearly not study drug related excluded', shows a frequency of 1.5% for Grade 3-4 AE 'transaminases increased' for nivolumab, and includes one auto-immune hepatitis event and one Drug induced liver injury (DILI) event.

8.5.1.2. Study CA209238

Hepatic select AEs (all-causality, any grade) were reported in 50 subjects (11.1%) in the nivolumab group and 116 subjects (25.6%) in the ipilimumab group.

Hepatic events considered drug–related by the investigator were reported for 41(9.1%) subjects for nivolumab and 96 (21.2%) for ipilimumab. Of these, 8 (1.8%) nivolumab and 49 (10.8%) ipilimumab subjects had Grade 3-4 events. For nivolumab one case of Grade 4 Drug-induced liver injury was reported.

The CSR states that '*12 subjects (29.3%) and 40 subjects (41.7%) received immune modulating medication for any grade drug-related hepatic select AEs in the nivolumab and ipilimumab groups,*

respectively.' This does not appear entirely consistent with the CSR table cited as reference, which shows 15 and 43 subjects respectively received immune modulating medication, of which 12 and 35 resolved.

From laboratory evaluations increases in liver function tests were primarily Grade 1/2. In the nivolumab group, there were no Grade 3/4 hepatic abnormalities reported in ≥ 5% of subjects.

Table 29: Laboratory evaluations of liver function tests

	Nivolumab 3 mg/kg N = 452	Ipilimumab 10 mg/kg N = 453
	N = 447	N = 444
ALT OR AST > 3XULN	20 (4.5)	68 (15.3)
ALT OR AST > 5XULN	8 (1.8)	53 (11.9)
ALT OR AST > 10XULN	4 (0.9)	28 (6.3)
ALT OR AST > 20XULN	2 (0.4)	14 (3.2)
	N = 447	N = 439
TOTAL BILIRUBIN > 2XULN	3 (0.7)	7 (1.6)
	N = 447	N = 439
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	0	5 (1.1)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	0	5 (1.1)

Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter.
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.

No subjects in the nivolumab group had concurrent ALT or AST elevation > 3 x upper limit of normal (ULN) with total bilirubin > 2 x ULN within 1 day or within 30 days of last dose of study therapy.

8.5.1.3. CA184029

Hepatic AEs considered immune-related were very common for ipilimumab (Any grade n = 118, 25%). There were 17 events with PT 'autoimmune hepatitis' (3.6%) and one event of DILI.

Grade 3 or 4 ALT abnormalities were reported in 10.3% and 0% of subjects in the ipilimumab and placebo groups, respectively; for AST abnormalities the frequencies were 8.8% and 0.2%.

8.5.2. Renal function and renal toxicity

8.5.2.1. Integrated safety analyses

The SCS compares 3 subjects (0.7%) with adverse reaction renal failure (reported as acute kidney injury) in Study CA209238 with 18 (0.6%) in the pooled nivolumab monotherapy population (n = 2950). The current Australian PI lists renal failure as 'uncommon' for nivolumab monotherapy.

Tubulointerstitial nephritis is listed for updated pooled nivolumab (4/2950, 0.1% in SCS) but was not recorded in Study CA209238.

8.5.2.2. Study CA209238

For renal select AEs, 6 subjects (1.3%) in the nivolumab group and 7 subjects (1.5%) in the ipilimumab group had AEs considered to be drug-related by the investigator; 4 in each group resolved. In the nivolumab arm there were 3 reports of drug-related acute kidney injury versus 0 for ipilimumab. One nivolumab subject received immune modulating medication. One subject in the nivolumab group was discontinued due to acute kidney injury considered drug related.

Laboratory evaluations

In both treatment groups, the majority of subjects with at least 1 on-treatment measurement had normal creatinine values during the treatment reporting period. Reported increases in creatinine were all Grade 1 or 2 (n = 4 for nivolumab, n = 5 for ipilimumab). No Grade 3 or 4 abnormalities were reported.

8.5.2.3. Study CA184209

Renal dysfunction was not reported with notable frequency for either study arm. Blood creatinine increased for 6 ipilimumab subjects (1.3%) versus 8 (1.7%) placebo subjects, and renal failure was reported for 4 (0.8%) ipilimumab versus 1 placebo patient; 4 placebo patients had nephrolithiasis.

8.5.3. Other clinical chemistry

8.5.3.1. Integrated safety analyses

Hyperkalaemia (all grades) is very common in the pooled nivolumab population (19.9%), as is hypokalaemia, hyponatraemia, and hypomagnesaemia. See Table 30. This is consistent with the current Australian PI.

Table 30: ADRs Investigations: Nivolumab monotherapy Study CA209238 and other tumour types

	CA209238 Nivolumab Monotherapy Arm n = 452 treated subjects				Pooled Nivolumab Monotherapy Population n = 2950 treated subjects[1]		
ADR[2,3,4]	No. of Subjects	% of subjects	Designation of frequency	Source Appendix for CA209238	No. of Subjects	% of subjects	Designation of frequency
Investigations[6]							
Increased AST	105/445	23.6	Very common	AM.2A-PI	849/2860	29.7	Very common
Increased ALT	113/447	25.3	Very common	AM.2A-PI	647/2868	22.6	Very common
Increased alkaline phosphatase	35/441	7.9	Common	AM.2A-PI	806/2856	28.2	Very common
Increased lipase	109/438	24.9	Very common	AM.2A-PI	265/1212	21.9	Very common
Increased amylase	68/400	17.0	Very common	AM.2A-PI	179/1094	16.4	Very common
Increased creatinine	54/446	12.1	Very common	AM.2A-PI	852/2875	29.6	Very common
Lymphocyte absolute (lymphopaenia)	119/446	26.7	Very common	AM.2A-PI	1179/2865	41.2	Very common
Leukocyte absolute (leukopoenia)	62/447	13.9	Very common	AM.2A-PI	425/2885	14.7	Very common
Platelet count (thrombocytopenia)	27/447	6.0	Common	AM.2A-PI	405/2879	14.1	Very common
Haemoglobin (anemia)	114/447	25.5	Very common	AM.2A-PI	1093/2881	37.9	Very common
Hypercalcaemia	14/434	3.2	Common	AM.2A-PI	280/2781	10.1	Very common
Hyperkalaemia	55/445	12.4	Very common	AM.2A-PI	562/2819	19.9	Very common

	CA209238 Nivolumab Monotherapy Arm n = 452 treated subjects				Pooled Nivolumab Monotherapy Population n = 2950 treated subjects[1]		
ADR[2,3,4]	No. of Subjects	% of subjects	Designation of frequency	Source Appendix for CA209238	No. of Subjects	% of subjects	Designation of frequency
Hypokalaemia	37/445	8.3	Common	AM.2A-PI	316/2819	11.2	Very common
Hypomagnesaemia[16]	39/441	8.8	Common	AM.2A-PI	364/2255	16.1	Very common
Hyponatraemia	72/446	16.1	Very common	AM.2A-PI	874/2821	31.0	Very common
Increased total bilirubin	33/446	7.4	Common	AM.2A-PI	294/2865	10.3	Very Common
Hypermagnesaemia[16]	20/441	4.5	Common	AM.2A-PI	111/2255	4.9	Common
Hypernatraemia	35/446	7.8	Common	AM.2A-PI	141/2821	5.0	Common
Hypocalcaemia	46/434	10.6	Very common	AM.2A-PI	523/2781	18.8	Very common
Weight decreased	5	1.1	Common	AM.8A-PI	61	2.1	Common
Hyperglycaemia[16]	Not measured	Not measured	-		132/322	41.0	Very common
Hypoglycaemia[16]	Not measured	Not measured	-		26/319	8.12	Common

[1] Monotherapy pooled group consists of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205, CA209141, CA209275, ONO-4538-12 and CA209032 (bladder and GC/GEJ 3L+ subjects)

8.5.3.2. Study CA209238

From the CSR: hyperkalaemia worsening change from baseline occurred in 55/445= 12.4%.

Other electrolyte changes were all very common as shown in Table 31.

Apart from hypernatraemia, frequencies were comparable or lower than for pooled data for nivolumab monotherapy.

Table 31: Electrolyte changes

All grades (1 to 4) %	Study CA209238	Pooled nivolumab[1]
Hypercalcaemia	3.2	10.9
Hypocalcaemia	10.6	17.2
Hyperkalaemia	12.4	18.8
Hypokalaemia	8.3	10.6
Hypermagnesaemia	4.5	4.4
Hypomagnesaemia	8.8	14.4
Hypernatraemia	7.8	5.1
Hyponatraemia	16.1	27.2

8.5.4. Haematology and haematological toxicity

8.5.4.1. Integrated safety analyses

The SCS showed, for updated pooled nivolumab monotherapy, a frequency of 336/2867 (11.7%, very common) for neutropenia (abnormal change from baseline) and 9 reports (0.3%, uncommon) for eosinophilia.

This is consistent with current Australian PI pooled nivolumab frequencies for the adverse reactions of neutropenia and eosinophilia.

In the current Australian PI there is a separate section for laboratory abnormalities worsened from baseline; in pooled nivolumab monotherapy the haematological abnormalities anaemia, thrombocytopenia, leukopenia, lymphopenia and neutropenia are all >10% that is, 'very common'.

8.5.4.2. Study CA209238

Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2.

Although changes from baseline grade are presented in the CSR, summaries for changes from baseline enabling comparison to the pooled nivolumab haematological abnormalities could not be located in the CSR for Study CA209238. From the CSR, change from baseline for neutropenia in Study CA209238 appears as 56/447 (12.5%), compared to 11.2% in the current PI.

No Grade 3/4 haematologic abnormalities were reported in ≥1% of subjects in either treatment group.

Table 30 shows comparable or lower frequencies (All grades) for the laboratory abnormalities anaemia, thrombocytopenia, leukopenia, and lymphopenia in Study CA209238, when compared to pooled nivolumab as shown in the current Australian PI.

8.5.4.3. Study CA184029

Low frequencies of subjects in both ipilimumab and placebo arms (most categories less than 1%) had Grade 3/4 abnormalities on study for any haematological laboratory test.

8.5.5. Other laboratory tests

8.5.5.1. Integrated safety analyses

Lipase and amylase increased were very common, 21.9% and 16.4% respectively, in subjects in the pooled nivolumab population provided in the SCS with the current submission.

The SCS appendices showing Grade 3/4 AEs 'excluding terms clearly not study drug related' records lipase increased and amylase increased for 4.9% and 2.4% nivolumab subjects in Study CA209238. This is comparable to the frequencies in the current PI for pooled nivolumab, 6.5% and 2.3% respectively.

8.5.5.2. Study CA209238

Lipase increased from baseline for 109/438 (24.9%) and amylase increased from baseline for 68/400 (17%), (all grades) for nivolumab in this study, slightly increased compared to 19.4% and 13.3% in the existing PI for pooled nivolumab monotherapy.

8.5.5.3. Study CA184029

Although not directly comparable, for context Grade 1/4 lipase frequencies were 26.9% for ipilimumab and 20.4% for placebo; Grade 3 or 4 lipase abnormalities were reported in 9.0% and 4.9% respectively. Grade 1/4 amylase on-study frequencies were 18.6% for ipilimumab and 9.3% for placebo; Grade 3 or 4 amylase abnormalities were reported in 2.2% and 0.8% of subjects in ipilimumab and placebo groups, respectively. No Grade 3/4 drug-related pancreatitis was reported.

8.5.6. Electrocardiograph findings and cardiovascular safety

8.5.6.1. Integrated safety analyses

No new information was provided.

8.5.6.2. Study CA209238

Cardiovascular adverse events were reported at low levels in this study; 5.5% in the nivolumab arm and 5.3% in the ipilimumab group.

In the nivolumab group there were 9 reports of AEs (all causality) of palpitations in women (5 considered drug related, none Grade 3-4), and 4 in men (1 considered drug-related, not Grade 3/4); 6 events of atrial fibrillation were reported, 3 in men (1 considered drug-related, not Grade 3/4,) and 3 (2 considered drug-related, neither Grade 3/4) in women subjects.

Other cardiac disorder PTs were reported as single events. There appeared to be no reports of myocarditis.

8.5.7. Vital signs and clinical examination findings

8.5.7.1. Integrated safety analyses

No new information was provided.

8.5.7.2. Study CA209238

Vital signs blood pressure (BP), heart rate, and body temperature together with pulse oximetry oxygen saturations were monitored and recorded for each patient at the study site as standard of care during screening and treatment visits, as safety monitoring by the treating physician. The values were listed in appendices to the CSR; no analysis was based on these records.

8.5.8. Immune-related adverse events

8.5.8.1. Integrated safety analyses

The updated pooled nivolumab data from other tumour types provided in the SCS included infusion-related reactions and hypersensitivity as common (2.9% and 1.4% respectively), consistent with the current PI. Anaphylactic reaction is rare.

Diarrhoea was very common and colitis common. Endocrine disorders hypothyroidism and hyperthyroidism were common, as was the respiratory disorder pneumonitis, and pyrexia.

Other Endocrine events hypophysitis, thyroiditis, adrenal insufficiency and hypopituitarism, diabetic ketoacidosis and diabetes mellitus were uncommon.

Overall the immune-related event profiles are unchanged, although some changes in frequency category are shown in the SCS for this submission compared to those shown in the current PI.

8.5.8.2. Study CA209238

Immune-mediated Adverse Events

IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose (that is, extended follow-up).

Endocrine

Endocrine events were included in IMAE analysis regardless of treatment, since these events are often managed without immunosuppression.

Specific evaluations for autoimmune endocrinopathies were not required or collected systematically, and specific laboratory criteria were not required to meet the case definition of endocrine IMAEs.

Table 32: Endocrine IMAEs

Disorder	Nivolumab 3mg/kg	Ipilimumab 10 mg/kg
Adrenal insufficiency	7 (1.5%)	19 (4.2%)
Discontinuation study therapy	1	4
Immune-modulating medication	6	13
Hypophysitis	9 (2.0%)	64 (14.1%)
Discontinuation study therapy	0	23
Immune-modulating medication	5	56
Hypothyroidism/thyroiditis	63 (13.9%)	41 (9.1%)
Discontinuation study therapy	1	4
Immune-modulating medication	4	6
Hyperthyroidism	39 (8.6%)	22 (4.9%)
Discontinuation study therapy	1	1
Immune-modulating medication	6	4
Diabetes mellitus	4(0.9%)	8 (1.8%)
Discontinuation study therapy	0	0

Disorder	Nivolumab 3mg/kg	Ipilimumab 10 mg/kg
Immune-modulating medication	0	0

Table 33: Non-endocrine IMAEs

PT: subjects with event (%)	Nivolumab 3mg/kg	Ipilimumab 10 mg/kg
Diarrhoea/colitis total	174 (38.5%)	263 (51.8%)
IMAES (immune-modulating medication)	29(6.4%)	144 (31.8%)
Discontinuation study therapy	9	79
Hepatitis total	54 (11.9%)	119 (26.3%)
IMAES (immune-modulating medication)	15 (3.3%)	43 (9.5%)
Discontinuation study therapy	3	23
Pneumonitis total	8 (1.8%)	14 (3.1%)
IMAES (immune-modulating medication)	8 (1.8%)	12 (2.6%)
Discontinuation study therapy	2	7
Nephritis and renal dysfunction total	17 (3.8%)	19 (4.2%)
IMAES (immune-modulating medication)	3 (0.7%)	1 (0.2%)
Discontinuation study therapy	0	0
Rash total	159 (35.2%)	215 (47.5%)
IMAES (immune-modulating medication)	73 (16.2%)	105 (23.2%)
Discontinuation study therapy	2	7
Hypersensitivity/infusion reactions total	13 (2.9%)	10 (2.2%)
IMAES (immune-modulating medication)	1 (0.2%)	2 (0.4%)
Discontinuation study therapy	0	0

8.5.8.3. Study CA184029

Any on-study imAEs were reported by 426(90.4%) versus 183 (38.6%).

Immune-mediated adverse reactions (imARs) were based on the investigator's assessment of immune-mediated aetiology.

The definition of imARs and the methodology for imAR analysis were developed between the sponsor and the US FDA for the first approval of 3 mg/kg ipilimumab monotherapy in the US.

These are tabulated below, for additional perspective on the frequencies reported in Study CA209238.

Table 34: imARs

	ipilimumab 10 mg/kg		placebo	
	Grade 2	Grade 3-5	Grade 2	Grade 3-5
Any on-study imARa	208 (44.2)	175 (37.2)	27 (5.7)	9 (1.9)
On-study enterocolitis imAR	58 (12.3)	67 (14.2)	12 (2.5)	3 (0.6)
On-study endocrinopathy imAR	84 (17.8)	38 (8.1)	2 (0.4)	0
On-study hepatitis imAR	21 (4.5)	50 (10.6)	1 (0.2)	1 (0.2)
On-study dermatitis imAR	95 (20.2)	18 (3.8)	9 (1.9)	0
On-study neuropathy imAR	1 (0.2)	5 (1.1)	0	0
On-study other imAR	11 (2.3)	27 (5.7)	4 (0.8)	6 (1.3)
Any on-study drug-related hypersensitivity or infusion reaction	25 (5.3)	5 (1.1)	1 (0.2)	0

Overall, ipilimumab in Study CA184029 was associated with high rates of immune-related adverse events with serious outcomes, many requiring discontinuation of study treatment and use of corticosteroids and/or hormone replacement therapy.

8.5.9. Other Events of Special Interest

8.5.9.1. Integrated safety analyses

No new information was provided.

8.5.9.2. Study CA209238

In the nivolumab group, OESI reports within 100 days of last dose were 4 subjects with pancreatitis and 3 subjects with uveitis. All resolved as of DBL.

In the ipilimumab group, OESI reports within 100 days of last dose were 1 subject with a Guillain-Barré Syndrome event (Miller Fisher Syndrome), 3 subjects with pancreatitis, 4 with uveitis, 1 with encephalitis, and 3 subjects with a myositis event (one each dermatomyositis, myositis, polymyositis). All resolved by DBL except Grade 4 drug-related Miller Fisher syndrome and Grade 2 drug-related dermatomyositis.

Overall there were no reports in the following OESI categories: myasthenic syndrome, demyelination, myocarditis, and rhabdomyolysis.

8.5.10. Other safety parameters: Immunogenicity

8.5.10.1. Integrated safety analyses

No new information: the SCS related only to findings from Study CA209238.

8.5.10.2. Study CA209238

Immunogenicity results were an exploratory endpoint.

ADA positive was defined as a subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titre to be at least 4-fold or greater than baseline positive titre at any time after initiation of treatment).

At the time of the interim CSR, incidence of ADA positive subjects were 10/426 (2.3%) and 3/405 (0.7%) in the nivolumab and ipilimumab groups respectively. ADA titres were low ranging from 1 to 8 following nivolumab and 1 to 64 following ipilimumab.

Three subjects in the nivolumab group were persistent positive (ADA-positive sample at 2 or more consecutive time-points, where the first and last ADA-positive samples are at least 16 weeks apart).

No subjects in either group had neutralizing anti-drug antibodies detected post-baseline.

For the nivolumab group, of the 13 subjects with a select adverse event of hypersensitivity/infusion reaction, 1/10 nivolumab ADA positive subject and 12/416 nivolumab ADA negative subjects experienced AEs in the hypersensitivity/infusion reaction category. This suggested no association between ADA and occurrence of hypersensitivity and infusion-related reactions.

ADA occurrence was depicted in relation to RFS per investigator for all nivolumab and ipilimumab ADA positive treated subjects. Subjects with nivolumab or ipilimumab ADA continued treatment with clinical benefit and presence of ADA did not appear to be associated with reduction in efficacy as shown by RFS.

8.5.10.3. Study CA184029

Results of anti-drug antibody (ADA) were consistent with observations in patients treated with ipilimumab for advanced melanoma. The formation of positive ADAs post-ipilimumab treatment was 4.9%, similar to the placebo treated group (4.5%). All subjects with positive ADA had low titres. No subjects with ADA had hypersensitivity or acute infusion reactions. Overall, the presence of ADA did not appear to be clinically significant.

8.6. Other safety issues

8.6.1. Safety in special populations

8.6.1.1. Intrinsic and extrinsic factors Study CA209238

In the nivolumab group, frequencies of all-causality and drug-related AEs for gender, race, age and region were similar to frequencies in the overall treated population.

For drug-related AEs, 82.5% male and 88.7% female subjects had any grade events; Grade 3/4 events occurred in 13.2% male, 15.9% female.

Frequencies for female subjects were higher for some PTs including any-grade fatigue 37% versus 33%, diarrhoea 28% versus 22%, arthralgia 15% versus 11%, myalgia 11% versus 5%, headache 13% versus 7%, and hypothyroidism 15% versus 7%.

Higher frequencies for any-grade drug-related AEs were also reported in the ≥ 75 age group (94.1%) versus < 65 (85.8%) and ≥ 65 to < 75 (81.6%); for Grade 3/4 the frequencies were 5.9%, 12.7% and 21.4% respectively.

A greater frequency of all-causality and drug-related AEs was reported in White subjects (97.4% and 86.4%) versus Asian subjects (87.5% and 66.7%).

Frequency of drug-related AEs was higher US and Canada (93.6%) versus Western Europe (82.8%), Eastern Europe (77.5%), or Asia (66.7%).

However the overall safety profile was not altered in subgroups.

8.6.1.2. Adverse events by baseline PD-L1 expression Study CA209238

No consistent differences were observed in the frequencies of all-causality AEs by PD-L1 expression subgroup (using either a 1% or 5% PD-L1 expression level).

For PD-L1 ≥1% rash occurred at 28%, versus PD-L1 < 1% frequency of 23 %; endocrine disorders overall were reported for 23% versus 16%, but other categories and individual PTs showed little difference by baseline PD-L1 1% expression .

For PD-L1 ≥ 5% rash frequency was 30% versus PD-L1 < 5% 24%; endocrine disorders overall were 22% versus 21% at the 5% PD-L1 expression level. Table S.10.20 of the CSR showed 24% of subjects in either category had a 'select' endocrine adverse event, with no consistent differences in disorder categories or PTs.

8.6.2. Safety related to drug-drug interactions and other interactions

No new information was provided.

8.6.3. Late-emergent adverse events

Drug-related AEs with an onset date > 100 days after last dose of study therapy were reported in 16 (3.5%) subjects in the nivolumab group, including 3 (0.7%) with Grade 3/4 events, and 22 (4.9%) subjects who received ipilimumab, which included 6 (1.3%) with Grade 3/4 events.

The latter included bone marrow failure (reported term; severe medullary aplasia) with onset on study Day 221; this subject died due to medullary aplasia 203 days after last dose of ipilimumab, as per Section 8.4.

In the nivolumab group the late onset drug-related AEs occurring in more than one subject included arthralgia (n = 2), and colitis (n = 2).

Other events reported for 1 subject included grade 3 pneumonitis and diarrhoea, grade 4 diabetic ketoacidosis, and grade 1 hypophysitis.

8.7. Post marketing experience

Not applicable to this indication in this submission.

8.8. Evaluator's overall conclusions on clinical safety

At data lock point that is, after 18 months follow-up, the rates of death were very similar. The majority of deaths in both treatment groups on Study CA209238 were due to disease, and occurred > 100 days after last study drug dose.

No new safety concerns about the types of adverse events were identified in nivolumab monotherapy adjuvant treatment compared to studies in other tumour types.

However it appears that some events, particularly immune-mediated AEs in GI, skin and endocrine categories, occurred with higher frequency in this study population than for the other previously approved indications.

If this extension to indications is approved, this should be adequately documented in the PI.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Table 35: Assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
The interim CSR for Study CA209238 showed improvement in RFS for adjuvant treatment with nivolumab compared to ipilimumab in subjects with completely resected Stage IIIB/C or Stage IV melanoma.	Nivolumab 3 mg/kg as adjuvant therapy compared to ipilimumab 10 mg/kg; HR = 0.65 (97.56% CI: 0.51, 0.83). · No OS outcomes available in interim study after 18 month follow-up. · Comparator not registered in

Indication	
Benefits	**Strengths and Uncertainties**
One-year RFS rates (95% CI) were nivolumab 70.5% (66.1, 74.5) versus ipilimumab 60.8% (61.8, 70.6).	Australia; extent of use where registered not clear. · Difficult to interpret the study data using perspective of currently used treatments for this patient group in Australia · Also unclear if PD-L1 status might be relevant for use in this population in the Australian context · No information available for resected Stage IIIA melanoma

9.2. First round assessment of risks

Table 36: Assessment of risks

Risks	Strengths and Uncertainties
No new safety concerns about the types of adverse events were identified in nivolumab monotherapy adjuvant treatment compared to studies in other tumour types. However immune-mediated AEs in GI, skin and endocrine categories appeared to occur with higher frequency in this study population compared to populations studied for previously approved indications. It was considered by the sponsor that this may be due to the intact immune system in patients in the adjuvant setting. Adjuvant melanoma subjects have a 13-45% higher predicted dose-normalised exposure relative to the advanced melanoma subjects.	The comparator was not directly relevant to current treatments in Australia. Toxicity was obviously less for nivolumab than for ipilimumab. It is less clear whether the trade-off of improved RFS versus risk of IMAEs is applicable to the entire patient group when any Stage III or Stage IV melanoma has been completely resected. The risk of recurrence has to be balanced against risk of severe or potentially life-threatening adverse drug reactions. ADR data as currently proposed for the PI might not adequately present safety risks for this patient group.

9.3. First round assessment of benefit-risk balance

From the data provided, there was improvement in RFS for nivolumab compared to ipilimumab for adjuvant treatment of melanoma combined with a known and better safety profile for nivolumab, and for this comparison the benefit-risk balance is considered positive.

This comparison is probably acceptable for extrapolation to the Australian context for the group studied, that is, adjuvant treatment of completely resected Stage IIIB/C and Stage IV melanoma, because the risk profile of nivolumab is well characterised and oncology teams are familiar with strategies for managing the immune-related adverse reactions. In general the risks are known and therefore acceptable, provided the frequencies of clinically relevant ADRs are adequately presented in the Product Information.

However, the extended indication requested is for adjuvant treatment of patients with completely resected Stage III or Stage IV melanoma, including those with completely resected Stage IIIA melanoma, who were not included in Study CA209238.

Adjuvant treatment for melanoma is intended to prevent recurrence. The risk-benefit balance might be less favourable for some in this group than for patients with advanced or metastatic melanoma, for whom nivolumab is already indicated.

While earlier use seems rational in view of the improved RFS, in patients with lower risk of melanoma recurrence the risk/benefit balance for adjuvant treatment might only become clear with additional data collection.

10. First round recommendation regarding authorisation

At this time the evaluator considers that recommendation for authorisation is reasonable for the extension of indication to the patient group with completely resected Stage IIIB/C and Stage IV melanoma, provided the limitations of the available data are made clear.

In particular the presentation of new data in the PI should state the period of follow-up, the current lack of OS outcomes, and a conservative presentation of the frequencies and severity of the immune-related ADRs reported in the interim CSR for Study CA209238, as well as noting that the study is ongoing.

11. Clinical questions

Evaluator questions during the evaluation period centred on correct location and confirmation of study data to support statements made in the CSR for the Interim Analysis.

11.1. Clinical questions

11.1.1. Pharmacokinetics

Not applicable

11.1.2. Pharmacodynamics

Not applicable

11.1.3. Efficacy

11.1.3.1. Eligibility

The study protocol stated that 'eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.'

Appendix 2.5 of the CSR shows by-subject listing of eligibility criteria for all enrolled subjects. The majority who failed criteria were not randomised.

Can the sponsor direct the evaluator to any additional information about the randomisation of a small number of subjects who failed inclusion/exclusion criteria?

11.1.3.2. Relevance of protocol deviations

All significant protocol deviations were provided.

Can the sponsor direct the evaluator to the rationale and/or criteria for specification of significant protocol deviations as 'relevant'?

11.1.3.3. RFS events

RFS was defined as the time between the date of randomisation and the date of first recurrence (local, regional or distant metastasis, confirmed by pathology and/or imaging), new primary melanoma, or death (whatever the cause), whichever occurs first. '*By-subject listing of recurrence- free survival, all randomised subjects*' in the CSR.

Please confirm that in the interim analysis all 44 deaths in the nivolumab arm, and 40/45 deaths in ipilimumab arm, were due to recurrence, but were not RFS events.

11.1.3.4. Duration of Follow-up

The CSR states '*Minimum follow-up (last subject's last randomisation date of 30-Nov-2015 to clinical cut-off date of 15-May-2017) for all randomised subjects was approximately 18 months*.'

Please direct the evaluator to data for duration of follow-up for the populations analysed for the interim CSR.

11.1.4. Safety

From the summary table of deaths, it appears there were 7 deaths in total other than those due to recurrences, 3 for nivolumab and 4 for ipilimumab. From '*Death listing, all enrolled subjects*', 7 deaths were identified but no detailed narratives were located.

The CSR states '*Safety narratives for deaths within 100 days of the last dose (excluding recurrence) in nivolumab-treated subjects are provided in Table S.6.'*

This table contains narratives for serious AEs. In the table provided for subjects receiving nivolumab, no narratives were identified as including death.

The 3 deaths within 100 days of last dose of nivolumab were due to 'disease', taken to mean melanoma 'recurrence', and therefore excluded from safety narratives.

Is it because there were no deaths within 100 days of nivolumab dosing, other than those due to recurrence of melanoma or new primary melanoma, that no safety narratives for deaths appear to be included in Table S.6?

Please direct the evaluator to the location in the dossier of any detailed narratives for deaths in either arm.

11.2. Sponsor response to questions

The answers were satisfactory and confirmed that the evaluator had interpreted the data as per sponsor intention.

In particular:

- The small numbers of subjects who were who randomised in spite of failing inclusion/exclusion criteria were not considered likely to have changes the outcome. This was accepted.
- The minimum follow-up for subjects in Study CA209238 was 17.5 months.

11.3. Additional expert input

Not applicable to this report.

12. Evaluation errata

Not applicable to this report.

13. Second round evaluation

Not applicable to this report.

14. Second round benefit-risk assessment

Not applicable to this report.

15. Second round recommendation regarding authorisation

Not applicable to this report.

16. Second round comments on product documentation

Not applicable to this report.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au