Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Nivolumab

Proprietary Product Name: Opdivo

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

August 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 AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

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	Neutralising anti-drug antibody
NED	No evidence of disease
OESI	Other event of special interest
OS	Overall survival
PP	Per protocol
PS	Performance status
RFS	Recurrence-free survival
SCS	Summary of clinical safety
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis
VPC	Visual predictive check

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	23 April 2018
Date of entry onto ARTG:	24 April 2018
ARTG number(s):	231867 and 231868
Active ingredient:	Nivolumab
Product name:	Opdivo
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd 4 Nexus Court Mulgrave VIC 3170.
Dose form:	Concentrate solution for intravenous infusion
Strengths:	40 mg / 4mL and 100 mg /10 mL
Containers:	Clear Type 1 glass
Pack size(s):	Pack of 1
Approved therapeutic use:	*Opdivo as monotherapy is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.*
Route of administration:	Intravenous (IV) infusion
Dosage:	The recommended dose of Opdivo as a monotherapy is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. The maximum treatment duration with Opdivo as monotherapy for adjuvant melanoma is 12 months.

Product background

This AusPAR describes the application by the sponsor to extend the indications of nivolumab (Opdivo) to include the adjuvant treatment of patients with completely resected Stage III or Stage IV melanoma, as monotherapy.

Opdivo is administered by intravenous infusion at a dose of 3 mg/kg every 2 weeks as monotherapy for the following indications: unresectable (Stage III) or metastatic (Stage IV) melanoma; locally advanced or metastatic squamous and non-squamous non-small cell lung cancer (NSCLC); advanced clear cell renal cell carcinoma; relapsed or refractory classical Hodgkin lymphoma (cHL), recurrent or metastatic squamous cell cancer of the head and neck and forurothelial cancer.

For metastatic melanoma with M1c disease or elevated lactate dehydrogenase (LDH), Opdivo in combination with ipilimumab, is administered intravenously every 3 weeks.

Drug class and therapeutic indication

Nivolumab is a fully humanised monoclonal antibody antineoplastic agent, a programmed death-1 receptor (PD-1) blocking antibody with World Health Organization (WHO) Anatomical Therapeutic Chemical (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.*

Regulatory status

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 LDH. See *Current indications approved in Australia* above for full indications.

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 in Australia.

Overseas regulatory history

At time of this submission to the TGA the following was known regarding overseas regulatory history of this product:

USA

As of 20 December 2017, the US FDA had approved the additional indication corresponding to this submission, resected melanoma in the adjuvant setting:

> *'Opdivo is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection'*[1]

Product Information

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

II. Registration time line

The following table captures the key steps and dates for this application (PM-2017-03752-1-4) and which are detailed and discussed in this AusPAR and Attachment 2.

Table 1: Registration time line for Priority review application PM-2017-03752-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	23 October 2017
Evaluation completed	17 March 2018
Sponsor's response to Delegate's Questions	9 April 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	18 April 2018
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	23 April 2018
Completion of administrative activities and registration on ARTG	24 April 2018
Number of working days from submission dossier acceptance to registration decision*	125

*Statutory time frame is 255 TGA working days.

[1] The US FDA application letter and full US FDA label is available from the accessdata.fda.gov website.

III. Quality findings

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

IV. Nonclinical findings

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

V. Clinical findings

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

Introduction

Clinical rationale

The sponsor 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.
- 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.

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 (EMA/CHMP/205/95/Rev.5), effective from 1 April 2018 at the EMA, and not yet adopted by TGA;

  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'.

Contents of the clinical dossier

Scope of the clinical dossier

- One interim pivotal company study report (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 Study 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 pharmacokinetics (PopPK) study report 930118022 v1.0 nivolumab PopPK analysis of adjuvant treatment nivolumab monotherapy in resected Stage IIIB/C or Stage IV melanoma. This includes a summary measure of simulated exposure 240 mg every 2 weeks versus 3 mg/kg every 2 weeks. The sponsor also requested that the PopPK evaluation of another of their TGA application's is cross-referred to when assessing the adjuvant melanoma application.

Paediatric data

No paediatric data were provided.

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

The application form states that 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.

Good clinical practice

According to each CSR, the studies were conducted in accordance with Good Clinical Practice (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 recurrence-free survival (RFS).

Pharmacokinetics

Studies providing pharmacokinetic data

The summary of clinical pharmacology for the adjuvant melanoma study refers to previous studies. The pharmacokinetics (PK) of nivolumab in solid tumours and classical Hodgkin lymphoma (cHL) has been characterised by PPK 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

No pharmacokinetic results excluded from consideration.

Evaluator's conclusions on pharmacokinetics

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

Adjuvant melanoma subjects have a 13 to 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.

Pharmacodynamics

Studies providing pharmacodynamic (PD) data

There were no specific PD studies provided with this submission.

Evaluator's conclusions on pharmacodynamics

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

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

Pharmacokinetics and pharmacodynamics: dose finding studies

The sponsor's Clinical Overview summarises previous dose-finding studies in melanoma, in particular Study CA209003 which was a Phase I safety, efficacy, PK study 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.

Evaluator's conclusions on dose finding for the pivotal studies

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

Efficacy

Studies providing efficacy data

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

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

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.

Evaluator's conclusions on 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 one year RFS rates (95% confidence interval (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 Overall survival (OS) for the placebo arm of Study CA184029 was 60% at 4 years.

Safety

Studies providing safety data

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 Common Terminology Criteria (CTC) grade laboratory parameters that worsened relative to Baseline (Standard International (SI) units)
- All Grade 3 or 4 adverse events (AEs)
- Any AEs leading to discontinuation, serious AEs (SAEs) and any Grade 3 or 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 PI
- Individual Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) broad and narrow scopes

The SCS included support for the proposed wording for 'Adverse reactions' in the EU Summary of Product Characteristics (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.

Patient exposure

The following table summarises the patient exposure to nivolumab in Study CA209238.

Table 3: Exposure to nivolumab and ipilimumab in 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 to 80.1	Not applicable	N = 453 Mean 41.07 (SD 18.340) Median 40 Range 9.8 to 70	Not applicable	N = 453

Safety issues with the potential for major regulatory impact

The sponsor's 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 (such as 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 characterisation.

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 30 ADRs Investigations: Nivolumab monotherapy CA209238 and other tumour types, for laboratory investigations from Study CA209238 compared to SCS pooled nivolumab data in Attachment 2.

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

Postmarketing data

Not applicable to this indication in this submission.

Evaluator's conclusions on 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.

First round benefit-risk assessment

First round assessment of benefits

Table 4 summarises the evaluator's assessment of benefits.

Table 4: First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
The interim CSR for 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. One year RFS rates (95% CI) were nivolumab 70.5% (66.1, 74.5) vs. ipilimumab 60.8% (61.8, 70.6).	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 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

First round assessment of risks

Table 5 summarises the evaluator's assessment of risks.

Table 5: First round 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 to 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.

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 adverse drug reactions (ADRs) are adequately presented in the Australian PI.

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.

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.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

The answers were satisfactory and confirmed that the evaluator had interpreted the data as per the sponsor's 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 CA209238 was 17.5 months.

VI. Pharmacovigilance findings

Risk management plan

- The most recently evaluated EU-RMP was version 6.2 (dated 27 January 2017; data lock point (DLP) 26 May 2016) and Australian Specific Annex (ASA) version 8.0 (dated 17 March 2017). In support of the extended indications, the sponsor has submitted EU-RMP version 12.0 (dated 20 September 2017; DLP 3 July 2017) and ASA version 10.0 (dated 2 October 2017).
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 6.

Table 6: Sponsor's summary of ongoing safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Immune-related pneumonitis	ü	ü	ü	ü
	Immune-related colitis	ü	ü	ü	ü
	Immune-related hepatitis	ü	ü	ü	ü

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
	Immune-related nephritis or renal dysfunction	ü	ü	ü	ü
	Immune-related endocrinopathies	ü	ü	ü	ü
	Immune-related skin adverse reactions	ü	ü	ü	ü
	Immune-related neurological adverse events*	ü	ü	ü	ü
	Other immune-related ARs (including Vogt-Koyanagi-Harada (VKH) syndrome and solid organ transplant rejection)	ü	ü	ü	ü
	Severe infusion reactions	ü	–	ü	ü
Important potential risks	Embryofetal toxicity	ü	–	ü	–
	Immunogenicity	ü	–	ü	–
	Cardiac arrhythmias (previously treated melanoma indication only)	ü	–**	ü	–
	Complications of allogeneic HSCT following nivolumab therapy	ü	ü	ü	ü
Missing information	Pediatric patients <18 years of age	ü	–	ü	–
	Patients with severe hepatic and/or renal impairment	ü	–	ü	–
	Patients with autoimmune disease	ü	–	ü	–
	Patients already receiving systemic immunosuppressants before starting nivolumab	ü	–	ü	–
	Elderly patients with: cHL ≥ 65 years of age SCCHN ≥ 75 years of age^	ü	–	ü	–
	Use in patients who have	ü	ü	–	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
	undergone influenza vaccination				

R = routine; A = additional; * Immune-related neurological adverse events (ASA only) are captured in the EU-RMP under 'other immune-related adverse events'.** The additional pharmacovigilance study, CA209037, was completed in October 2016. Cardiac arrhythmia continues to be monitored in multiple ongoing Phase III clinical trials.

Routine pharmacovigilance is proposed for all safety concerns. The sponsor is conducting a range of additional pharmacovigilance studies which have been considered in previous RMP evaluations by the TGA.

Additional risk minimisation activities include a healthcare professional (HCP) communication tool which is a management guide for immune-related adverse reactions and a patient alert card. The HCP tool has been revised to remove the indications and instead refer HCPs to the most recent PI for the approved indications.

New and outstanding recommendations

In the rolling question response the sponsor committed to updating the ASA, PI and Consumer Medicine Information (CMI). The updated versions of the PI and CMI have been provided and updated as requested to include 'Bullous pemphigoid'. For the ASA, it is acceptable for the updates to be included the next time it is revised.

Wording for conditions of registration

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

The suggested wording for conditions of registration is:

> *The Opdivo EU-Risk Management Plan (RMP) (version 12.0, 20 September 2017; DLP 3 July 2017), with Australian Specific Annex (version 10.0, dated 2 October 2017), included with submission PM-2017-03752-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

The following wording is recommended for the PSUR requirement:

> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).*
>
> *Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.*

VII. Overall conclusion and risk/benefit assessment

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

Quality

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

Nonclinical

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

Clinical

Efficacy

Study CA209-238 (CheckMate 238)

The results in the dossier are for the cut-point (database lock) as at June 2017.

Published as:

- Weber M et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. NEJM. DOI: 10.1056/NEJMoa1709030. Published online: September 10, 2017, at NEJM.org.

Design

Phase III, double blind, placebo controlled, multicentre (130 sites), multinational (25 countries) study with enrolment March 2015 to September 2015.

The following table summarises the study design (Table 7).

Table 7: Study CA209-238 design

Patients	Nivolumab: 453, high-dose ipilimumab: 453 *Inclusion criteria* Complete resection of · Stage IIIb/c (nodal disease>1 mm) · Stage IV 15+ years (although all enrolled patients were 18+ years) ECOG: 0 or 1 *Exclusions* Ocular/uveal melanoma Autoimmune disease Any disease requiring treatment with systemic steroids (10+ mg prednisone per day) Any prior systemic therapy for melanoma (interferon allowed if >6 months before randomisation

Intervention	Nivolumab: 3 mg/kg every 2 weeks (q2w) Maximum of 1 year or until unacceptable toxicity or patient withdrawal from study
Comparator	Ipilimumab: 10 mg/kg every 3 weeks (q3w) for 4 doses, then every 12 weeks (q12 w) Maximum of 1 year; or until unacceptable toxicity or patient withdrawal from study
Endpoints	*Primary* RFS (recurrence or death) *Secondary* · OS · RFS stratified by PD-L1 expression *Exploratory* · Distant metastasis-free survival (Stage III) · RFS/OS stratified by BRAF

Randomisation was stratified by Stage (IIIB/IIIC, IVM1a/IVM1b, IVM1c) and PD-L1 status, tumour cells only (< 5%, 5+ %)

Follow-up for RFS:

- during the treatment period: every 12 weeks
- during follow-up period (1-2 years): every 12 weeks
- during follow-up period (2-5 years): every 6 months

Stage IV: Patients with completely resected Stage-IV disease would be eligible for nivolumab under the existing melanoma indication. The sponsor has stated that these patients were excluded from the registration trials in Stage-IV melanoma (no lesion to measure at baseline); and, consequently were included in this study.

Sample size

- Power: 85%; alpha: 0.05, 2-sided (accounting for the interim analysis, alpha = 0.043, 2-sided)
- Minimal clinically important differences (MCID): Hazard ratio (HR) (RFS) = 0.75
- 450 RFS events expected at final RFS analysis; minimum of 36 months follow-up; 900 patients randomised (that is, 50% expected to recur at 36 months)

Protocol amendment January 2017

- An interim analysis of RFS after all study participants had a minimum of 18 months of follow-up (NEJM paper, CSR submitted in the dossier; data cut-point: June 2017).
- Approximately 350 RFS events were anticipated at this analysis.
- The stopping boundaries at the interim analysis were derived based on the exact number of RFS events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries; alpha = 0.022, 2-sided. (No interim analysis of OS was planned to be performed at this time).

- On 30 June 2017, the independent Data Monitoring Committee (DMC) reviewed the interim data (as per the January 2017 protocol amendment) and confirmed that the pre-specified boundary for RFS was crossed with no new safety signals identified that would affect continuation of the study. An interim CSR reporting primary endpoint results and safety was produced (this application). The study is ongoing.

Schedule of analyses

- Interim analysis on RFS (primary endpoint) when all patients followed-up for 18 months (see January 2017 protocol amendment, above: NEJM paper, CSR submitted in this application; data cut-point: June 2017).
- Final analysis on RFS (primary endpoint) when all patients followed-up for 36 months.
- Interim analysis on OS (secondary endpoint) when all patients followed-up for 36 months.
- Final analysis on OS (secondary endpoint) when all patients followed-up for 48 months (expected 2020).

Patient disposition (as at June 2017)

The following table summarises treatment discontinuations.

Table 8: Treatment discontinuations

	Nivolumab N = 453	Ipilimumab N = 453
Completed treatment[a]	61%	27%
Disease recurrence	27%	22%
Toxicity	9%	46%
Withdrew consent, and similar	2%	3%

Median duration of therapy: nivolumab (11.5 months) ipilimumab (2.7 months)

Patients not continuing in the study is summarised in Table 9 below.

Table 9: Patients not continuing in study

	Nivolumab 13%	Ipiliumab 16%
Death	10%	10%
Withdrew	3%	5%
Loss to FU, etc	<1%	1%

Median follow-up as at 12-Jun-2017 was 19.5 months

At database lock (June 2017), no patients were still on treatment.

Censored, mainly because of the event of interest, recurrence had not been observed.

- Nivolumab: 299 (66%)

· Ipilimumab: 247 (55%)

Subsequent treatment is summarised in Table 10 below.

Table 10: Subsequent treatment

	Nivolumab N = 453	Ipiliumab N = 453
Any	129 (28.9%)	171 (37.7%)
RT	24 (5.3%)	26 (5.7%)
Surgery	69 (15.0%)	64 (14.1%)
Systemic	90 (19.9%)	136 (30.0%)
ipilimumab	35 (7.7%)	15 (3.3%)
nivolumab	17 (3.8%)	43 (9.5%)
pembro	10 (2.2%)	63 (13.9%)
BRAF inhibitor	41 (9.1%)	40 (8.8%)
MEK/NRAS inhibitor	31 (6.8%)	40 (8.8%)

Other systemic treatments included PD-L1 inhibitors, interferon, interleukin, various combinations, and various experimental medicines are outlined below (see Table 11, Baseline characteristics).

Table 11: Baseline characteristics

	Nivolumab N = 453	Ipilimumab N = 453
Median age, range	56 years (19, 83)	54 years (18, 86)
Men	57%	59%
Stage		
IIIb	36%	33%
IIIc	45%	48%
IV	18%	19%
LN involvement, Stage III		
Micro	34%	37%
Macro	59%	59%
Not reported	7%	5%

	Nivolumab N = 453	Ipilimumab N = 453
Ulceration, Stage III		
Yes	42%	37%
No	55%	59%
Not reported	4%	4%
PD-L1		
< 5 %	61%	63%
5+ %	34%	34%
Not reported	6%	3%
BRAF		
Yes	41%	43%
No	44%	47%
Not reported	15%	10%

Results (database lock: 12 June 2017)

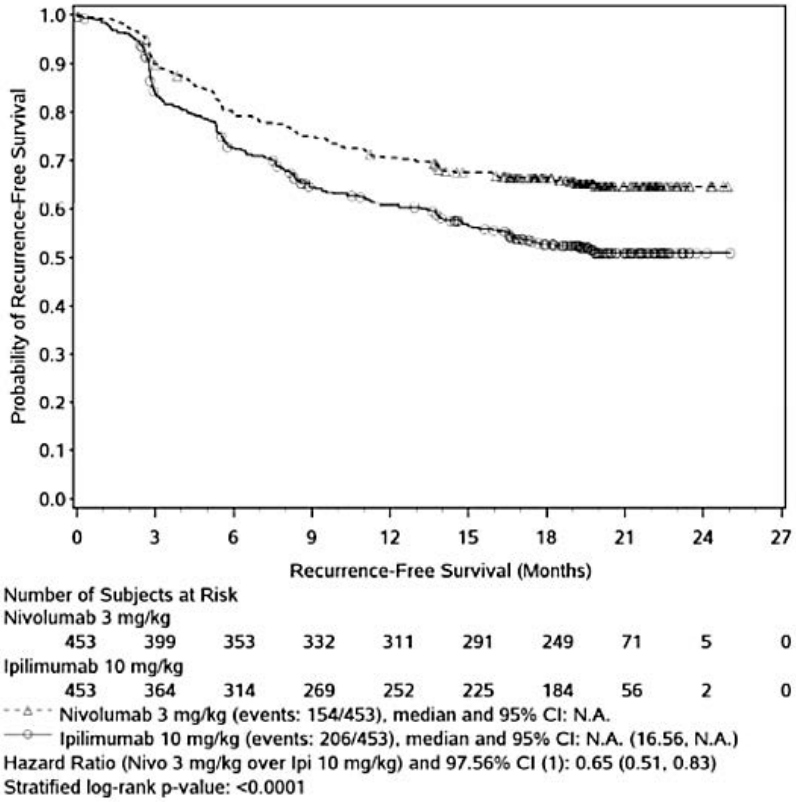
Pre-specified interim analysis, protocol amendment January 2017

Recurrence free survival (primary endpoint) is summarised in Table 12 and Figure 1 below.

Table 12: Recurrence free survival (primary endpoint)

	Nivolumab N=453	Ipilimumab N=453
Events, n(%)	154 (34%)	206 (46%)
Median (95% CI)	Not reached	Not reached
HR (97.56% CI)	0.65 (0.51, 0.83); p < 0.0001	
12 month rate (95% CI)	71% (66, 75)	61% (56, 65)
18 month rate (95% CI)	66% (62, 71)	53% (48, 57)

Figure 1: Kaplan-Meier RFS plot All randomised subjects



The following table summarise the Subgroup analysis by stage, RFS.

Table 13: Subgroup analysis by stage, RFS

	Nivolumab events/patients	Ipilimumab events/patients	HR (95% CI)
IIIb	41/163	54/148	0.67 (0.44, 1.00)
IIIc	79/204	109/218	0.65 (0.49. 0.87)
IV M1a-M1b	25/62	35/66	0.63 (0.38, 1.05)
IV M1c	8/20	8/21	1.00 (0.37, 2.66)

The following table summarise the *Subgroup analysis by PD-L1, RFS*.

Table 14: Subgroup analysis by PD-L1 expression, RFS

	Nivolumab events/patients	Ipilimumab events/patients	HR (95% CI)
5+%	31/152	57/154	0.50 (0.32, 0.78)
< 5%	123/300	149/299	0.71 (0.56, 0.90)
1+%	80/287	133/307	0.56 (0.42, 0.73)

	Nivolumab events/patients	Ipilimumab events/patients	HR (95% CI)
< 1%	65/140	67/133	0.82 (0.59, 1.16)
10+%	20/106	39/105	0.45 (0.26, 0.77)
< 10%	125/321	161/335	0.71 (0.56, 0.89)
Missing	9/26	6/13	0.78 (0.28, 2.19)

The following table summarise the *Subgroup analysis by BRAF status, RFS*.

Table 15: Subgroup analysis by BRAF status, RFS

	Nivolumab events/patients	Ipilimumab events/patients	HR (95% CI)
Mutation	63/187	84/194	0.72 (0.52, 1.00)
No mutation	67/197	105/214	0.58 (0.43, 0.79)
Missing	24/69	17/45	0.83 (0.45, 1.54)

Distant metastasis-free survival (exploratory endpoint)

Table 16: Distant metastasis-free survival Patients with Stage III disease at study entry

	Nivolumab N=369	Ipilimumab N=366
Events, n(%)	93 (25%)	115 (31%)
Median (95% CI)	Not reached	Not reached
HR (97.56% CI)	0.73 (0.55, 0.95)	
12 month rate (95% CI)	80% (76, 84)	73% (68, 78)
18 month rate (95% CI)	75% (70, 79)	67% (61, 71)

Quality of life

Quality-of-life scores in the two groups remained close to baseline values without any clinically meaningful changes with respect to the score on the EORTC QLQ-C30[2] Global Health Status or on any of the individual scales, as well as to scores on the EQ-5D utility index and the EQ-5D visual analogue scale.[3]

[2] The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients.
[3] EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D consists of a descriptive system and the EQ visual analogue scale (VAS).

EORTC QLQ-C30 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.

In Australia, the most relevant comparison is to placebo, not ipilimumab. The sponsor provided an overlay of QoL curves for nivolumab in CM-238 (CA209238) versus placebo in Study CA184029. EORTC QLQ-C30 scores were similar for nivolumab in Study CA209238 and placebo in Study CA184029; however this analysis is not definitive, given the well-known problems with indirect comparisons across trials.

Safety

Adverse events reported are summarised in Table 17 below.

Table 17: All grades AEs for nivolumab and ipilimumab

	Nivolumab, n = 452		Ipilimumab, n = 453	
	All grades	Grade 3/4	All grades	Grade 3/4
Any AE	438 (96.9%)	115 (25.4%)	446 (98.5%)	250 (55.2%)
Treatment-related AEs	385 (85.2%)	65 (14.4%)	434 (95.8%)	208 (45.9%)
AEs leading to discontinuation	44 (9.7%)	21 (4.6%)	193 (42.6%)	140 (30.9%)
Treatment-related AEs leading to discontinuation	35 (7.7%)	16 (3.5%)	189 (41.7%)	136 (30.0%)
Serious AEs	79 (17.5%)	48 (10.6%)	183 (40.4%)	144 (31.8%)

Serious: death, illness requiring hospitalization, events deemed life-threatening, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect or medically important condition.

Deaths that occurred during the study are described in Table 18 below.

Table 18: Deaths

	Nivolumab N=452	Ipilimumab N=453
Disease related	41 (9.1%)	41 (9.1%)
Toxicity of medicine	0	2 (0.4%)
Other	3 (0.7%)	2 (0.4%)
Total	44 (9.7%)	45 (9.9%)

Immune-related AEs included:

- hypothyroidism 11.1%
- hyperthyroidism 8.4%
- hypophysitis 1.5%
- thyroiditis 2.2%
- diarrhoea 24.3%
- rash 28.5%
- pruritus 23.2%
- arthralgia 12.6%

Condition of registration

Postmarketing studies

Submit the final clinical report and datasets at the time of the final analysis for overall survival (OS) of Study CA209238, entitled '*A Phase III, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab versus Ipilimumab after Complete Resection of Stage IIIB/C or Stage IV Melanoma in Subjects who are at High Risk for Recurrence (CheckMate 238)*', to revise the product label with mature OS data.

Final Report Submission is expected September 2020.

Risk management plan

See *Pharmacovigilance findings* above.

Risk-benefit analysis

Delegate's considerations

Benefit risk balance

Condition

Stage III melanoma patients are a heterogeneous group; for example, the 5 year death rate for IIIa patients (included in Study CA184-029 [ipilimumab versus placebo] but not Study CM-238 [nivolumab versus ipilimumab]) is about 25% (from the placebo arm of Study CA184-029). IIIa is N1a or N2a: clinically occult lymph node involvement (that is, detected by sentinel lymph node biopsy).

There are various estimates of 5 year relapse free survival for Stage III melanoma; for example, IIIa: 63%; IIIb: 32%; IIIc: 11%.[4]

[III] a, b, c depends on:

- micro (occult) versus macro lymph node (LN) involvement
- number of LNs
- clumping of LNs

[4] Romano E, Scordo M, Dusza SW, Coit DG, Chapman PB. Site and timing of first relapse in Stage III melanoma patients: implications for follow-up guidelines. J Clin Oncol 2010;28: 3042-7

- ulceration and thickness of the primary lesion

A patient's decision on whether to have adjuvant treatment will depend on their preferences/values, age, comorbidities, and the risk of recurrence (which can vary, as above).

Current treatment options

The term 'adjuvant treatment' refers to treatment offered after initial primary therapy, to further delay relapse and to improve overall survival.

Currently, the only registered option for adjuvant treatment of such patients in Australia is Interferon alpha-2b which required 4 weeks of intensive intravenous therapy (daily infusions Days 1 to 5 for 4 weeks) and then three subcutaneous injections per week for an additional 48 weeks. The benefits were limited with an improvement in RFS demonstrated in two studies and a pooled analysis, but no benefit in OS identified in the pooled analysis.[5] Adverse effects were common (for example, dose modifications occurred in 65% of patients in the meta-analysis). Interferon is mainly of historical interest.

Ipilimumab does not have marketing approval as an adjuvant treatment for melanoma in Australia. A randomised, controlled trial (RCT) of ipilimumab 10 mg/kg every 3 weeks then 3 monthly for a total of 3 years demonstrated improved RFS and OS compared with placebo, but with the expected toxicity associated with ipilimumab (Study CA184029).[6] Ipilimumab is approved in the US for adjuvant treatment of melanoma.

In Australia, the current management of patients with Stage III melanoma is to enrol them in a clinical trial or watch and wait.

Benefits and associated uncertainties

RFS

Study CA209238 (Checkmate-238): Stage-IIIb, IIIc, and fully-resected Stage IV; nivolumab (n = 435) versus ipilimumab (n = 453).

The CSR was submitted to regulatory agencies (FDA, EMA and the TGA) based on a planned interim analysis (data cut-point: June 2017), after all patients had a minimum follow-up of 18 months. No patients were still on study treatment. The independent DMC reviewed the interim data (as per the January 2017 protocol amendment) and confirmed that the pre-specified boundary for RFS was crossed with no new safety signals identified that would affect continuation of the study.

The proposed indication is for all Stage III (which would include IIIa); and fully resected Stage IV. [CA184-029 (ipilimumab versus placebo) enrolled Stage IIIa, IIIb, IIIc, but not Stage IV.]

CA209-238

After a minimum of 18 months follow-up (median = 19.5 months), patients in the nivolumab arm had fewer recurrences/deaths, 34.0% (n = 154/453), compared with patients in the ipilimumab arm: 45.5% (n = 206/453). HR for RFS (pre-specified primary endpoint) for nivolumab versus ipilimumab was 0.65 (0.51, 0.83), $p < 0.0001$. This HR was further from 1.0 than the pre-specified MCID (0.75), used in the sample size calculation.

[5] Kirkwood JM, Manola J, Ibrahim J, Sondak V, Ernstoff MS, Rao U. 'A pooled analysis of eastern cooperative oncology group and intergroup trials of adjuvant high-dose interferon for melanoma.' Clin Cancer Res 2004; 10(5):1670–1677

[6] 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

Median RFS was not reached in either arm. The Kaplan-Meier RFS rate (accounting for censoring) at 18 months was 66% in the nivolumab arm versus 53% in the ipilimumab arm.

These RFS results were from a pre-specified interim analysis, with data cut-point June 2017 based on a protocol amendment from January 2017 (p-values and CIs for RFS were appropriately adjusted for multiplicity). The final RFS analysis is planned when patients have been followed for 36 months.

Study CA184029 compared ipilimumab to placebo in the adjuvant setting: HR (RFS) =0.76 (0.64, 0.89); 5 year RFS rate: 41% versus 30%. These results are relevant for an indirect comparison of nivolumab to placebo; with the usual caveat about indirect comparisons across different trials (for example, Study CA184029 enrolled Stage-IIIa patients, but not fully resected Stage IV; Study CA209-238 enrolled fully resected Stage-IV, but not Stage IIIa.)

OS

No results have been reported for OS (secondary endpoint) from the pivotal registration trial (Study CA209238).

Interim OS analyses are planned after 36 months follow-up, with final OS analyses planned after 48 months follow-up (expected 2020; see Condition of registration).

When available, interpretation of OS results might be complicated by the post-recurrence treatments received by patients. For example, at the June 2017 data cut-point, 20% of patients in the nivolumab arm and 30% of patients in the ipilimumab arm had additional systemic therapies.

Based on Study CA184029 (the ipilimumab versus placebo trial), RFS benefit in this setting seems to translate into OS benefit.

Subgroup analyses

Benefit for nivolumab was reported for RFS in nearly every subgroup tested, including those defined according to age, sex, disease stage, microscopic versus macroscopic nodal disease, ulceration status of the primary tumour, BRAF status and various PD-L1 expression cut-points.

Harms and associated uncertainties

The pivotal Study CA209238 showed that nivolumab is less toxic than ipilimumab (10 mg/kg). This was expected.

Nivolumab was discontinued for adverse events in 9% of patients (ipilimumab around 40%).

Median time on treatment was 11.5 months in the nivolumab arm and 2.7 months in the ipilimumab arm.

No new types of adverse effects for nivolumab were identified in this setting.

Benefit-risk balance

The decision about whether to undertake adjuvant treatment with nivolumab (infusions every 2 weeks for 12 months) is a decision for each individual patient in consultation with their medical oncologist. Adjuvant treatment is secondary prevention. Some patients, who decide to have adjuvant treatment (perhaps one-third, depending on the subgroup of Stage III disease), would never have had a recurrence (without adjuvant treatment) by 5 years; and so will be exposed to the possible toxic effects of nivolumab without benefit.

Nivolumab will be prescribed by medical oncologists, who are well versed in the benefit-risk trade-offs involved in the adjuvant treatment of any cancer and will be able to

assist patients with decisions about whether to embark on adjuvant nivolumab treatment of their (completely resected) melanoma.

Patients, who decide to have adjuvant treatment, would need to be aware of the symptoms of the various immune related toxicities so that they can seek immediate treatment.

Request for ACPM advice

This application was not referred to the Advisory Committee on Medicines for advice.

Response from sponsor

Responses to questions raised by the Delegate of the 2 April 2018

[information redacted]

The FDA approved indication for the use of nivolumab as an adjuvant therapy in patients with melanoma based on the results from Study CA209238 is as follows:

> *Opdivo is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.*

The sponsor considers that the definition of patients with completely resected Grade 3 or Grade 4 melanoma is identical to patients '*with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection'*.

In view of this, the sponsor would be open to discussing the wording of the indication with the TGA when the PI is being finalised.

Advisory Committee Considerations

This application was not referred to the TGA's Advisory Committee on Medicines for advice.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of approve the registration of AUST R 231867 Opdivo nivolumab 40 mg in 4 mL (10 mg/mL) concentrated solution for IV infusion vial AUST R 231868 Opdivo nivolumab 100 mg in 10 mL (10 mg/mL) concentrated solution for IV infusion vial, indicated for:

> *Opdivo as monotherapy is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.*

Specific conditions of registration applying to these goods

1. Submit the final clinical report at the time of the final analysis for overall survival (OS) of Trial CA209238, entitled 'A Phase III, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab versus Ipilimumab after Complete Resection of Stage IIIB/C or Stage IV Melanoma in Subjects who are at High Risk for Recurrence (CheckMate 238).'
2. The Opdivo EU-Risk Management Plan (RMP) (version 12.0, 20 September 2017; DLP 3 July 2017), with Australian Specific Annex (version 10.0, dated 2 October 2017), included with submission PM-2017-03752-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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