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 2016

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
ACPM	Advisory Committee on Prescription Medicines
ACSOM	Advisory Committee on the Safety of Medicines
ADA	anti-drug antibody
AE	adverse event
AUC	area under the plasma drug concentration-time curve
Cmax	maximum concentration of drug in serum
CMI	Consumer Medicines Information
CSR	clinical study report
DILI	drug induced liver injury
EC50	half maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FDA	Food and Drug Administration (US)
HCP	healthcare professional
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IASLC	International Association for the Study of Lung Cancer
IV	intravenous
LDH	lactic dehydrogenase
mAb	monoclonal antibody
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
NSQ NSCLC	non-squamous non-small cell lung cancer
ORR	objective response rate
OS	overall survival

Abbreviation	Meaning
PD-1	programmed death-1
PFS	progression free survival
PI	Product Information
Q2W	once every two weeks
SAE	serious adverse event
SJS	Stevens-Johnson syndrome
SQ NSCLC	squamous non-small cell lung cancer
t 1/2	half life
TEN	toxic epidermal necrolysis
ULN	upper limit of normal
WHO	World Health Organization
WT	wild type

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	7 January 2016
Date of entry onto ARTG	11 January 2016
Active ingredient:	Nivolumab
Product name:	Opdivo
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd 4 Nexus Ct Mulgrave VIC 3170
Dose form:	10 mg/mL concentrate solution for infusion
Strengths:	One 4 mL vial contains 40 mg of nivolumab One 10 mL vial contains 100 mg of nivolumab
Container:	10-cc Type I flint glass vials, stoppered with 20 mm FluroTec film coated butyl rubber stoppers, and sealed with 20 mm crimp seals with Flip-Off seals
Pack sizes:	40 mg of nivolumab in 4mL of concentrate solution for infusion (10 mg in 1 mL). Pack of one vial containing 4 mL. 100 mg of nivolumab in 10mL of concentrate solution for infusion (10 mg in 1 mL). Pack of one vial containing 10 mL.
Approved therapeutic use:	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.
Route of administration:	Intravenous (IV) infusion (must not be administered as an intravenous push or bolus injection)
Dosage:	For monotherapy: 3 mg/kg administered IV over 60 minutes every 2 weeks For combination therapy: 1 mg/kg administered intravenously

	over 60 minutes every 3 weeks for the first 4 doses in combination with ipilimumab 3 mg/kg
ARTG numbers:	231867 (40 mg in 4 mL) 231868 (100 mg in 10 mL)

Product background

This AusPAR describes the application by Bristol-Myers Squibb Australia Pty Ltd to register a new chemical entity nivolumab (trade name: Opdivo), a monoclonal antibody (mAb) against programmed death-1 (PD-1), proposed to be used for the treatment of patients with unresectable or metastatic melanoma or squamous cell non-small cell lung cancer (SQ NSCLC). Nivolumab is also being tested in patients with non-squamous non-small cell lung cancer (NSQ NSCLC), renal cell carcinoma, and various other cancers.

Unresectable or metastatic melanoma

The sponsor has applied for an indication in unresectable or metastatic melanoma. By metastatic melanoma, this is taken to mean distant metastatic melanoma (Stage IV), not regional and distant metastasis (Stages III and IV).

There are 3 subclasses of Stage IV melanoma. The subclasses are based on where the metastases are located and the level of lactic dehydrogenase (LDH).

- M1a: the tumour has metastasised to distant skin, the subcutaneous layer or to distant lymph nodes. LDH is normal.
- M1b: the tumour has metastasised to the lungs. LDH is normal.
- M1c:
  - the tumour has metastasised to organs other than the lungs, and LDH is normal; or
  - there are any distant metastases with elevated LDH.

Table 1 shows M stage categories for cutaneous melanoma.

Table 1. M stage categories for cutaneous melanoma.

M	Site	Serum LDH[b]
M0	No distant metastases	Not applicable
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastases	Elevated

[a] Balch CM, Gershenwald JE, Soon S-J, et al. Final version of 2009 AJCC Melanoma Staging and Classification. J Clin Oncol 2009;27:6199-6206.

[b] LDH - Lactate dehygrogenase

Some prognostic factors in cutaneous melanoma are listed:[1]

- **Stage of disease** (integrating: primary tumour thickness, ulceration and mitotic rate; regional lymph node status; presence of distant metastases; LDH level).
- **Age** (advancing age is associated with worse prognosis).
- **Gender** (male gender is associated with worse prognosis).
- Anatomic location
- Mutation status (for example, BRAF and NRAS)

The prognostic value of interactions between melanoma and the immune system has also been studied. Lo and Fisher noted in a recent review of melanoma:[2]

> *The importance of immune responses in melanoma has long been appreciated, with reports of spontaneous melanoma regressions published more than 50 years ago. The cancer immunosurveillance hypothesis, which posits that adaptive immunity can prevent cancer development and progression, was supported by observation of higher melanoma incidence in immunosuppressed patients. Early discovery of immune infiltrates and tumor-specific antibodies as positive prognostic factors provided additional evidence of immune interactions with melanoma.*

Treatment of advanced melanoma has changed with recent availability of ipilimumab (anti CTLA-4 mAb), pembrolizumab (anti PD-1 mAb), vemurafenib (BRAF inhibitor), dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor).[3] (In the US and Japan, nivolumab became available in 2014.)

The US National Comprehensive Cancer Network (NCCN) Melanoma Guideline version 3 (2015) preferred certain regimens to treat metastatic or unresectable melanoma,

[1] Buzaid and Gershenwald. Tumor node metastasis (TNM) staging system and other prognostic factors in cutaneous melanoma. Up-to-date Topic 7618 version 33.0.
[2] Lo JA, Fisher DE. The melanoma revolution: from UV carcinogenesis to a new era in therapeutics. *Science* 346: 945-949 (2014).
[3] Curti B. Rapid evolution of combination therapy in melanoma. *NEJM* 371: 1929-1930 (2014).

depending on: (a) BRAF V600 tumour status, and (b) the patient's clinical stability. The NCCN did recommend nivolumab (among other options) as first line therapy in all settings, but did not endorse nivolumab + ipilimumab combination therapy.

It may be argued disease control by BRAF inhibitors is transient. With combined BRAF and MEK inhibition, progression has been delayed for many: median progression free survival (PFS) is now ~9-10 months. In Combi-V,[4] in the combination arm, median duration of response was 13.8 months; in Combi-D,[5] it was 9.2 months. These median durations of response are in the context of a relatively high response rate. Only patients with BRAF V600 mutant tumours have these options.

Squamous non-small cell lung cancer

The two major types of lung cancer are small cell lung cancer and NSCLC (~81% of lung cancers). Six per cent of lung cancer originates from other cell types. The World Health Organization (WHO)/International Association for the Study of Lung Cancer (IASLC) histological classification of NSCLC is:

- Squamous cell carcinoma (20% of lung cancers; ~25% of NSCLC)
- Adenocarcinoma (38% of lung cancers; ~47% of NSCLC)
- Large cell carcinoma (5% of lung cancers; ~6% of NSCLC)
- Other (18% of lung cancers; ~22% of NSCLC)

These histological subtypes arise in different anatomical compartments, for example, SQ NSCLC may often arise from the central airway compartment (so may be close to large vessels, etcetera). Some tumours have mixed histology.

As well as histology, key influences on choice of initial therapy for advanced disease are:

- extent of disease (for example, number and site of metastases);
- presence of symptoms related to a specific metastatic site;
- presence of driver mutations (for example, EGFR; ALK; ROS1);[6] and
- the patient's overall condition and co-morbidities.

Influences on choice of subsequent therapy for advanced disease are similar. Another influence is choice of prior treatment (that is, the need for a non-cross resistant approach).

Treatment of advanced NSCLC aims to prolong survival and maintain quality of life, while minimising side effects of treatment. Almost all patients with advanced NSCLC eventually develop progressive disease.

Treatment of advanced NSCLC involves surgery, radiotherapy and/or chemotherapy. In local guidelines provided by the Cancer Council Australia, each stage (I-IV) of NSCLC is divided into 'operable' and 'non-operable'. Surgery may not be possible due to comorbidity, poor lung function, tumour location or patient choice.

[4] Robert C, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* 372: 320-30 (2015).
[5] Long G, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med.* 371: 1877-1888 (2014).
[6] Driver mutations/aberrations in EGFR and ALK are more typical in adenocarcinoma than squamous cell NSCLC: Korpanty GJ, et al. Biomarkers that currently affect clinical practice in lung cancer: EGFR, ALK, MET, ROS-1, and KRAS. *Frontiers in Oncology* 4: 204 (2014).

Targets and mechanism of action

Nivolumab is a humanised monoclonal antibody (IgG4/kappa isotype)[7] against the cell surface receptor PD-1. Nivolumab inhibits PD-1 – PD-L signalling. There are two PD-1 ligands, PD-L1 and PD-L2.

PD-1's role is summarised by Pardoll[8] as to limit the activity of T cells in tissues at the time of an inflammatory response to infection and to limit autoimmunity.

The proposed mechanism by which nivolumab acts is to allow the immune system to engage with and 'reject' the tumour, as outlined below. There is a recent synopsis published.[9]

Multiple mechanisms undermine an adaptive immune response to cancer. An adaptive immune response is regulated by 'immune checkpoints' that allow negative feedback, dampening the response. This regulation is protective in important scenarios, for example, in the context of infection, constraining immune responses to limit tissue damage; or in the context of self-antigen, preventing autoimmunity. However, immune checkpoints may also subvert an effective anti-tumour response.

A component of one immune checkpoint is induction of PD-1 expression on T cells after antigen exposure. Subsequent binding by PD-L1 or -L2 will inhibit T cell function. It has been argued that T cells in the tumour microenvironment could up-regulate PD-1 due to persistence of tumour antigen. However, for a negative signal to be delivered via PD-1's intracellular domain, engagement with PD-L1 or -L2 is required.

Overexpression of PD-L1 has been reported in tumours, including melanoma[10] (PD-L1 can be constitutively expressed, or induced by interferon producing T cells; IFN-g is reported to up-regulate its expression on tumour cell lines). PD-L1 may also be found on immune cells that infiltrate the tumour.

PD-1 – PD-L signalling between T lymphocytes and tumour cells (or other immune cells in the tumour microenvironment) may attenuate anti-tumour responses, via inhibitory signalling to the T cell (an intrinsic effect on the T cell) and/or promotion of regulatory T cells ('Tregs') (an extrinsic mechanism that suppresses T cell function).

Blockade of PD-1 – PD-L signalling therefore encourages adaptive tumour immunity, in that it relieves this inhibitory signalling.

Regulatory status

The following is a discussion relevant to the international regulatory status of Opdivo at the time of submission to the TGA.

The sponsor's submission to register nivolumab, dated 6 January 2015, requested approval for use in advanced melanoma. Based on the sponsor's summary of outcomes in a Phase III study in SQ NSCLC, the TGA allowed the scope of the submission to enlarge.

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[7] IgG4 has lower affinity than IgG1 for FcgRs, but it binds to RI, RIIA, RIIB, RIIC and RIIIAV158, suggesting cell-mediated effects are possible: Bruhns P, et al. Specificity and affinity of human Fcg receptors and their polymorphic variants for human IgG subclasses. *Blood* 113: 3716-3725 (2009). IgG4 does not activate complement. The ACPM Summary states that the mechanism of action of nivolumab does not involve ADCC (or CDC).

[8] Pardoll D. The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer* 12: 252-264 (2012).

[9] Wolchok J, Chan T. Cancer: antitumour immunity gets a boost. *Nature* 515: 496-498 (2014).

[10] PD-L1 may be expressed on tumour infiltrating immune cells, and/or neoplastic cells themselves (not to mention native tissue stroma): Taube J, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. *Clin Cancer Res.* 20: 5064-74 (2014).

Pembrolizumab is another mAb in the same class, that is, anti PD-1 mAb. It was registered in April 2015 for use in advanced melanoma.

Nivolumab does not have orphan status in Australia.

Table 2 shows the international regulatory history (US, EU and Australia) for Opdivo at time of submission to TGA. Other countries in which the drug has been approved include Canada, Japan, Switzerland, and Israel.

Table 2. International regulatory history for Opdivo at time of submission to TGA.

Country	Indication number/ Submission Date Actual / *Planned*	Approval Date Actual / *Best Planned*	Indication
US	1) 30 Jul 2014 2) 22 Dec 2014 3) 27 Feb 2015 4) 30 Mar 2015 5) 02 July 2015 6) 22 July 2015 7) 15 Sep 2015	1) 22 Dec 2014 2) 04 Mar 2015 *3) Nov 2015* 4) 30 Sep 2015 5) 09 Oct 2015 *6) Jan 2016* *7) Mar 2016*	1) 2/3 Line melanoma ORR 2) Previously treated Squamous NSCLC *3) 1L mono melanoma 066* 4) 1L melanoma combination with Yervoy (069) 5) Non SQ NSCLC (057) *6) combo melanoma w/IPI 067* *7) Renal Cell (025) OS*
EU	1, 2) 04 Sept 2014 (2 parallel submissions) 3) 08 July 2015 4) 08 July 2015 5) 13 Oct 2015	1) 19 Jun 2015 2) 20 July 2015 *3) 1Q2016* *4) 1Q2016* *5) 3Q2016*	1) Advanced metastatic melanoma 2) Previously treated Sq NSCLC (name reconciliation approved 24 Sep 2015) *3) 1L melanoma combination with Yervoy* *4) Non Sq NSCLC* *5) Renal*
Australia	1, 2, 3) 07 Jan 2015 4) 31 Aug 2015 *5) 07 Dec 2015*	*1, 2, 3) Feb 2016* *4) Best: Feb 2016 Base: Sep 2016* *5) 4Q 2016*	*1) monotherapy advanced melanoma* *2) combination with Yervoy 1L melanoma* *3) Previously treated SQ NSCLC;*

Country	Indication number/ Submission Date Actual / *Planned*	Approval Date Actual / *Best Planned*	Indication
			4) NSQ NSCLC: TGA allowed addition as parallel submission *5) Renal 2/3L*

Product information

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

II. Quality findings

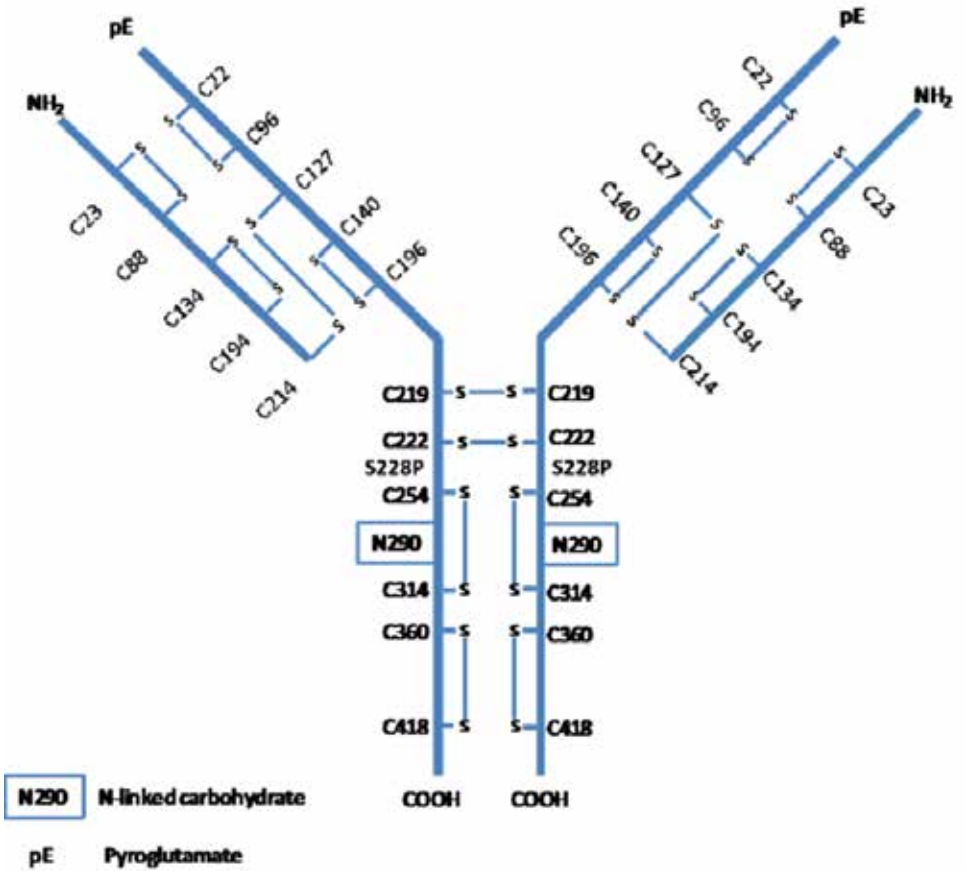
Drug substance (active ingredient)

Nivolumab is a fully human monoclonal antibody of the IgG4 class comprising four polypeptide chains: two identical heavy chains of 440 amino acids and two identical kappa light chains of 214 amino acids, which are linked through inter chain di-sulphide bonds. It is similar to many other monoclonal antibody products and is manufactured by conventional established methods.

The predominant product has a molecular formula of $C_{6462}H_{9990}N_{1714}O_{2074}S_{42}$ (with heavy chain N-terminal pyro-glutamate, without C-terminal lysine and with G0F/G0F glycol-form) with a calculated molecular weight of 146,221 Da.

The cDNA derived amino acid sequences of heavy and light chains of nivolumab are shown below (Figure 1).

Figure 1. Structure of nivolumab.



The drug substance is manufactured from cell culture supernatants. Cell banking processes are satisfactory.

The cell culture material from the production bioreactor is processed by centrifugation for cell removal followed by depth filtration to remove remaining cells and cell debris to produce clarified bulk. A subsequent ultrafiltration (UF) step is used to concentrate the clarified bulk, which is then filtered through depth filters followed by membrane filters to produce concentrated clarified bulk that is appropriate for transfer to the purification area.

Nivolumab is purified using a series of chromatographic and filtration steps. The downstream process was designed to reduce product and process related impurities and to clear potential adventitious viral agents. The downstream manufacturing process includes three chromatographic steps: a Protein A chromatography step, a hydrophobic interaction chromatography (HIC) and a cation exchange (CEX) chromatography step. The downstream processing steps also include a viral inactivation (VI) step and a viral filtration (VF) step. All viral/prion safety issues have been addressed, including use of animal derived excipients, supplements in the fermentation process and in cell banking.

After the VF step, an UF/diafiltration (DF) step produces a product pool that is designated as unformulated bulk (UFB) drug substance. The addition of Polysorbate 80 to the UFB drug substance generates formulated bulk drug substance.

Each lot of formulated bulk drug substance is filtered into bioprocess containers. The drug substance is stored at 2°C to 8°C.

The drug substance is stable at the long term storage condition (5°C) for up to 31 months. Slight changes in SE-HPLC, CE-SDS and iCIEF results are incorporated into the specifications. Based on these real time data, an initial shelf life of 24 months is proposed for drug substance stored under refrigeration (2°C to 8°C) and protected from light. The stability trials are carried out in compliance with the ARGPM Guidance 14 and are satisfactory.

Drug product

Formulation

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/4 mL (100 mg/mL), is a clear to opalescent, colourless to pale yellow liquid which may contain light (few) particulates. The drug product is a sterile, non pyrogenic, single use, preservative free, isotonic aqueous solution for IV administration. Nivolumab injection may be administered undiluted at a concentration of 10 mg/mL or further diluted with 0.9% sodium chloride injection (sodium chloride 9 mg/mL (0.9%) solution for injection) or 5% dextrose injection (50 mg/mL (5%) glucose solution for injection) to nivolumab concentrations as low as 1 mg/mL.

The biological activity is tested by three assays: binding activity enzyme linked immunosorbent assay (ELISA), potency ELISA, and cell based bioassay. Each of the three proposed assays measures a relevant biological effect of the product at different levels in its mechanism of action.

Stability

An initial shelf life of 24 months is proposed for drug product stored 2°C to 8°C based upon the assessment of stability data. This is acceptable.

Stability studies for registration of the drug product are being conducted on eight batches of nivolumab injection, 100 mg/10 mL (10 mg/mL) and three batches of 40 mg/4 mL (10 mg/mL), in accordance with ICH (International Conference on Harmonisation) stability guidances. Stability samples were stored in primary package components representative of the intended commercial package and data generated in these studies were assessed by the proposed acceptance criteria in the proposed specifications.

Long term stability studies have also been done in compliance with ICH Q1A (R2).[11] Studies evaluating photo stability and freeze/thaw cycling have also been completed.

Additionally, a stress followed by long term storage study was performed. Additional detail and results are described in the sections that follow. Samples were stored horizontally, inverted, or upright in the same 10 mL glass vials used for drug product.

Nivolumab Injection, 100 mg/10 mL, (10 mg/mL), is a stable product as demonstrated by the available real time stability data for eight drug product batches stored at the long term condition of 5°C for 36 months (one batch), 24 months (one batch), and 18 months (six batches).

Stability studies at the accelerated condition of 25°C/60%RH were conducted through 6 months. Whereas some changes were observed in charged species (by iCIEF), size distribution (by SE-HPLC) and purity (by SDS-PAGE/CE-SDS), with two exceptions, results met all proposed acceptance criteria. As expected for a protein therapeutic, similar but greater changes were observed in drug product stored for up to six months at the stress

[11] European Medicines Agency, "ICH Topic Q 1 A (R2) Stability Testing of new Drug Substances and Products (CPMP/ICH/2736/99)", August 2003.

condition of 40°C/75% relative humidity. These results are consistent with changes observed in the drug substance stability studies and indicate that appropriate stability indicating assays were used.

Data from photo stability studies show that nivolumab injection is sensitive to high intensity fluorescent visible light and ultraviolet-A irradiation and thus must be protected from light.

However, room temperature/room light studies showed that nivolumab injection is not susceptible to degradation from exposure to ambient room light for up to one month. Four cycles of freezing and thawing did not adversely affect the stability of the drug product.

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the substance and to establish a shelf life.

The real time data submitted support a shelf life of 2 years at 2°C to 8°C.

Quality summary and conclusions

The quality aspects data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

There are outstanding issues: one manufacturer's clearance is about to expire; an update is required.[12]

There are no objections to the registration of:

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

It is, however, a condition of registration that, as a minimum, the first five independent batches of

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

imported into/manufactured in Australia are not released for sale until samples and the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratory Branch (LB).

The sponsor should supply:

- Certificates of Analysis of all active ingredient (drug substance) and final product.
- Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
- Evidence of the maintenance of registered storage conditions during transport to Australia.
- 5 vials of each batch for testing by the TGA LB together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

[12] This issue was resolved by the end of TGA's evaluation.

III. Nonclinical findings

Introduction

Nivolumab (Opdivo) is a human monoclonal IgG4 antibody directed against programmed cell death receptor PD-1 which is expressed in CD4+ and CD8+ T cells, NK cells, B cells and monocytes. Nivolumab is intended to be used for the treatment of unresectable or metastatic melanoma alone or in combination with ipilimumab, a human cytotoxic T lymphocyte antigen 4 (CTLA-4) blocking antibody.

The proposed monotherapy dosage for nivolumab is 3 mg/kg IV infusion (over 1 h) every 2 weeks. For combination therapy, the proposed dosage is 1 mg/kg IV nivolumab combined with ipilimumab 3 mg/kg IV every 3 weeks for the first 4 doses followed by nivolumab 3 mg/kg IV as a single agent every 2 weeks.

The submitted dossier was in accordance with the relevant ICH guidelines for the nonclinical assessment of anticancer and biotechnology derived pharmaceuticals.[13] All pivotal safety studies were conducted under Good Laboratory Practice (GLP) conditions.

Pharmacology

Primary pharmacology

Rationale and mechanism of action

PD-1 interaction with its ligands, PD-L1 and PD-L2, leads to down regulation of T cell responses, including T cell proliferation and cytokine production, and limits immune destruction of tissues. Nivolumab binds to PD-1 and inhibits the interaction of PD-L1 and PD-L2 ligands with the PD-1 receptor. This has the potential to promote immune responses such as antigen specific T cell responses to both foreign and self-antigens leading to enhanced tumour immunosurveillance and anti-tumour immune response.

In vitro studies

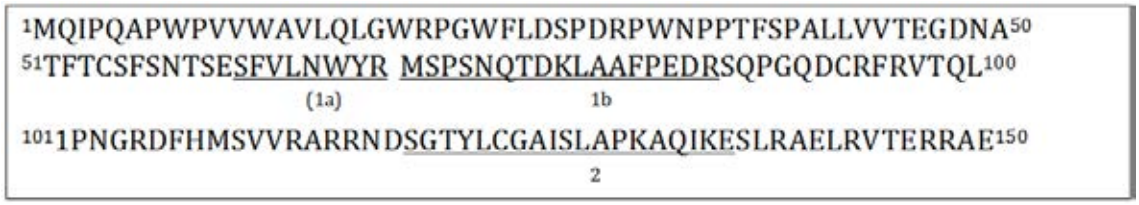
Evidence of pharmacological effects of nivolumab comes from in vitro binding and functional studies. The binding studies showed that nivolumab could bind to PD-L1 receptor and block the receptor binding to its ligands (see below) whereas the functional studies showed that nivolumab could activate T cells. These effects occurred at nanomolar concentrations.

The in vitro studies showed evidence of nivolumab binding to human and Cynomolgus monkey PD-1 receptor with high affinity (KD 3.06 and 3.92 nM, respectively) and a half maximal effective concentration (EC50) of 0.39 nM in human PD-1-Ig fusion protein. Nivolumab also bound to PD-1 transfected CHO cells (EC50 = 1.7 nM) and activated human CD4+ T cells expressing cell surface PD-1 (EC50 = 0.64 nM). After binding to PD-1, nivolumab blocked the binding of the ligands PD-L1 and PD-L2 to human PD-1 receptor with high potency (a low EC50 of 1 nM for both). Consistent with the expression of PD-1 on activated lymphocytes, immunoreactivity was observed in lymphocyte populations of human and Cynomolgus monkey tissues in cross-reactivity studies. Species specificity was also seen in the binding: nivolumab did not bind to rat or rabbit (or mice, see In vivo studies, below) PD-1 receptor.

[13] European Medicines Agency, "ICH Topic S 9 Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008)", December 2008; European Medicines Agency, "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)", June 2011.

The amino acid sequences recognised by nivolumab were shown to be residues 62-69 (1a), 70-86 (1b), and 118-136 (2) (see Figure 2, underlined). The binding of nivolumab to antigen was dependent on glycosylation of PD-1. Peptide 1a has the strongest affinity to nivolumab.

Figure 2. Amino acid sequences recognised by nivolumab.



The binding to PD-1 was selective as shown by the absence of nivolumab binding to related molecules such as CD28, CTLA-4, inducible T cell co-stimulator (ICOS), or B and T lymphocyte attenuator (BTLA). In vitro studies also showed that nivolumab did not mediate antibody dependent cell mediated cytotoxicity (ADCC) in activated human CD4+ T cells or exhibit complement dependent cytotoxicity (CDC) in target activated CD4+ (PD expressing) T cells.

PD-1 inhibition by nivolumab resulted in enhanced T cell activation in an allogeneic Mixed Lymphocyte Reaction (MLR) as measured by increased interferon gamma (IFN-γ) secretion and T cell proliferation. Nivolumab (up to 30 μg/mL) also enhanced Cytomegalovirus (CMV) lysate induced antigen specific stimulation of memory T cell mediated IFN-γ production by human peripheral blood mononuclear cells (PBMCs) isolated from donors previously infected by CMV. EC50 values of nivolumab were reported to be 0.001-0.018 μg/mL for this effect. During chronic virus infections, such as Hepatitis C Virus (HCV), PD-1 receptor expression is reported to be high on CD8+ T lymphocytes correlating with T cell exhaustion. Nivolumab reversed this exhaustion (CD8+ T cells produced 2.4-2.7 fold increase in IFN-γ and tumour necrosis factor-alpha [TNF-α] in the presence of nivolumab compared to control). The enhancing effect of PD-1 blockade on T cell function required T cell receptor stimulation.

A study conducted with PBMCs isolated from HIV seronegative stage 3/4 resected melanoma patients who had been vaccinated with gp100 and/or MART-1 peptide analogs showed that nivolumab augmented the absolute numbers of CD31, CD41, CD81 and gp100/MART-1 MHC:peptide tetramer CTLs. This correlated with increased frequencies of IFN-γ secreting antigen specific cells and augmented lysis of gp1001/MART-11 melanoma targets. PD-1 blockade also increased the fraction of antigen specific CTLs that recognized melanoma targets by degranulation, suggesting increased recognition efficiency for cognate peptide. The increased frequencies and absolute numbers of antigen specific CTLs by nivolumab resulted from increased proliferation, not decreased apoptosis. Kinetic analysis of cytokine secretion demonstrated that PD-1 blockade increased both type-1 and type-2 cytokine accumulation in culture.

Nivolumab (up to 100 μg/mL) did not affect ex vivo cytokine expression (release of IFN-γ, TNF-α, IL-2, IL-4, IL-6, and IL-10) in human peripheral blood cells.

In vivo studies

Mouse tumour models were used to show evidence that PD-1 blockade in vivo could result in anti-tumour activity. Nivolumab does not recognise mouse PD-1 and hence the studies were conducted with an anti-mouse PD-1 antibody 4H2. This antibody 4H2 bound to CHO cells expressing murine PD-1 (EC50 = 2.9 nM) and blocked the binding of mouse PD-L1 ligand (EC50 = 3.6 nM).

In an in vivo tumour model in mice (C57BL/6 mice injected with MC38 colon carcinoma cells), 4H2 (10 mg/kg intraperitoneal (IP), started on the same day of MC38 cell injection

and on Days 3, 6 and 10) inhibited tumour growth (83% inhibition on Day 21). In the same model, administration of 4H2 (3, 10 or 30 mg/kg IP 6 days after MC38 cells and on Days 10 and 13) resulted in a dose dependent tumour growth inhibition, and 10-20% of treated animals were tumour free on Day 59, while all control animals died or were killed by day 27 due to large tumours.

Anti-tumour activity was also seen in another mouse model (A/J mice injected with SA1/N murine fibrosarcoma cells) after the administration of 4H2 (0.3-30 mg/kg IP every 3 or 4 days after SA1/N injection). The administration of 4H2 (0.3-30 mg/kg IP), in the same model, even after tumour development showed Anti-tumour activity.

Limited efficacy was observed in a mouse myeloma model injected with J558 myeloma cells. Tumour growth was similar in treated and control groups except for one instance of delayed tumour growth and two animals (out of 8) of tumour regression in the nivolumab-treated group (10 mg/kg IP on days 10, 13 and 17). 4H2 did not show anti-tumour activity in four other tumour models in mice (renal cell carcinoma [Renca], 4T1 breast carcinoma, CT26 colon carcinoma or B16F10 melanoma cells). Nor was the combination of 4H2 and an anti-mouse CTLA-4 mAbs (9D9) inhibited tumour growth in the mouse B16-F10 and J558 models.

The above studies showed that PD-1 blockade with a surrogate of nivolumab (4H2) in mice could result in Anti-tumour activity though not in all mouse tumour models including a melanoma (B16F10) model.

Ipilimumab is a recombinant, humanised monoclonal antibody (IgG1 kappa) that binds to the cytotoxic T lymphocyte associated antigen 4 (CTLA-4; also known as CD152) and blocks binding of its natural ligands, B7-1 (CD80) and B7-2 (CD86). This blockade results in potentiation of tumour specific T cell activation and proliferation.

Since nivolumab and ipilimumab act by different mechanisms for Anti-tumour activity (via PD-1 and CTLA-4 blockade, respectively), combining these two agents is expected to be clinically beneficial. However, there were no studies in animal tumour models to show better efficacy for the combination than either drug alone.

Secondary and safety pharmacology

There is no standard secondary PD study. This is considered acceptable for a biotechnology derived product, especially when the intended use is in patients with unresectable or metastatic melanoma. As indicated above, nivolumab does not bind to CD28, CTLA-4, ICOS or BTLA.

Cynomolgus monkeys were used in safety studies on nivolumab (a safety pharmacology study as well as toxicity studies). The Cynomolgus amino acid sequence is highly homologous to human PD-1 and nivolumab has binding affinity to Cynomolgus monkey PD-1 similar to the affinity to human PD-1. Considering this and the fact that nivolumab does not recognise mouse PD-1 receptor, Cynomolgus monkeys are considered an appropriate species for studies (including toxicity studies) on nivolumab.

Investigation of safety pharmacology was limited to a single dose study in Cynomolgus monkeys. The study was conducted mainly to assess cardiovascular effects (including BP and ECG) in addition to changes in clinical signs, body weight and body temperature. In this study, there were no treatment related changes after a single administration of nivolumab at 1 or 10 mg/kg IV. No other safety pharmacology studies were conducted, but the above study and toxicity studies showed no clinical signs of CNS, cardiovascular or respiratory effects at exposures up to 27 and 35 times the clinical exposure based on maximum concentration of drug in serum (Cmax) and area under the plasma drug concentration-time curve (AUC), respectively.

Pharmacokinetics

Pharmacokinetic (PK) studies were performed in the Cynomolgus monkey, which is used in the toxicity studies. In monkeys, after a single or repeated IV administration of nivolumab (1 to 50 mg/kg), plasma nivolumab concentrations were dose-dependent and did not show any significant difference between males and females. The volume of distribution (Vd) was small (~0.05 L/kg). Total clearance (CL) was slow (generally 0.16-0.3 mL/h/kg), and the elimination half- life (t1/2) ranged from 5 days (at 10 mg/kg) to 11 days (at 50 mg/kg). The Vd and CL in monkeys were similar to the values observed in patients (Vd 82.8-112.7 mL/kg; CL 0.13-0.19 mL/h/kg), while the elimination t1/2 in monkeys was shorter than that in patients (median t1/2 24.8 days).

There were no studies on tissue distribution, metabolism or excretion. Being a protein, nivolumab is expected to be degraded to small peptides and amino acids, and eliminated. The protein nature also suggests that nivolumab is not expected to cause or be subject to pharmacokinetic drug-drug interactions.

Plasma concentrations in monkeys increased with repeated once weekly or twice weekly dosing, which is expected given the long elimination t1/2. However, there was no (or only minor) drug accumulation in the 1 month combination study of nivolumab (10 or 50 mg/kg/week IV) with ipilimumab (3 or 10 mg/kg /week). Plasma nivolumab concentrations were not markedly reduced in most animals by anti-drug antibodies (ADA).

Toxicology

Acute toxicity

In a single dose toxicity study in Cynomolgus monkeys, there were no treatment related effects on clinical signs, body weight or clinical chemistry after IV administration of nivolumab at 1 or 10 mg/kg. High doses (50 mg/kg IV twice weekly) were also well tolerated in repeat dose studies.

Repeat dose toxicity

Repeat dose toxicity studies included a 30 day and a 3 month study in Cynomolgus monkeys with nivolumab alone (doses: 1, 10 and 50 mg/kg IV weekly in the 1 month study and 10 and 50 mg/kg IV twice weekly in the 3 month study) and a 4 week study in the same species with the nivolumab (10 and 50 mg/kg IV weekly) and ipilimumab (3 and 10 mg/kg IV weekly) combination.

Relative exposure

In the repeat dose toxicity studies in monkeys, the systemic exposure at the highest dose was 35 fold higher than the clinical exposure based on AUC (Table 3). The respective maximum exposure based on Cmax in the 1 and 3 month studies was 16 and 27 fold higher than the clinical exposure (Cmax in patients after the 9th dose: 132.0 µg/mL; animal and human Cmax comparison not shown in the table below). Serum nivolumab concentrations (measured for up to 24 h after dosing) in the combination study with ipilimumab in week 4 were lower than the levels in monkeys dosed with nivolumab alone because of minimal or no accumulation in the combination study.

Table 3. Relative exposure in repeat-dose toxicity studies.

Species	Study	Dosing Frequency	Dose (mg/kg)	AUC_{0-168h} (µg·h/mL)	Exposure ratio#
Monkey (Cynomolgus)	1 month	Once weekly	1	2590	0.17
			10	43950	2.9
			50	210000	14
	3 months	Twice weekly	10	117000	7.6
			50	531000	35
Human (Cancer patients)	MDX1106-03 [CA209003]	Once every 2 weeks	3	30640*	–

= animal AUC x 2 : human serum AUC; * AUC_{0-336h} after the 9^{th} dose.

In both repeat dose studies with nivolumab alone, a diffuse pattern of inflammatory cell infiltration was seen in many organs or tissues, but the lesions were minimal or mild and also seen in control animals with a lower incidence for most tissues. The inflammatory changes were not associated with other signals of organ toxicity (for example, plasma transaminases, creatinine and urea). This effect may be related to PD-1 blockade by nivolumab and is consistent with data in PD-1 pathway deficient mice which showed higher incidences and/or severities of spontaneous inflammatory lesions in the liver, kidney and paws (joints and skin) when compared to those of wild type animals in a study conducted by the sponsor.

Lymphocytes phenotyping showed no effects on the population of peripheral blood B (CD20+) or T (CD3+) cells, T cell subsets (CD3+CD4+ or CD3+CD8+), NK cells (CD3-CD16+), or monocytes (CD3-CD14+). In the 3 month study, analysis of additional T cell subsets showed increased blood CD4+ and CD8+ effector memory T cells (CD28-CD95+), as well as blood and spleen CD8+ central memory T cells (CD28+CD95+) in both dose groups, compared with the control group. The increase was probably related to the pharmacological activity of nivolumab since inhibition of PD-1 prevents the dampening of the immune response and therefore permits proliferation and differentiation of memory T cells.

Ventricular premature contractions (PVCs) were seen in two high dose females, but not in males, in the 3 month study. It was unclear whether the finding was treatment-related or just a normal variant.

The serum T3 level in week 13 was decreased in high dose females (by 28%) in the 3 month study. However, there were no changes in males, there was no histological evidence of thyroid effects, T4 levels were unaffected, and TSH was decreased in females only in week 17 (after the recovery period). No changes in thyroid hormones were detected in the 1 month study. The decrease in T3 in the 3 month study was probably not related to treatment.

Receptor occupancy investigation 4 weeks after cessation of treatment was conducted in the 1 month study. A substantial proportion of CD3+ cells in all dose groups exhibited

reduced binding of biotin-conjugated nivolumab, indicating receptor occupancy by the administered drug.

In the 4-week combination study with weekly dosing of nivolumab and ipilimumab, inflammatory changes in the large intestine were seen in both treated groups. The lesions were characterised by lymphoplasmacytic/lymphocytic/histiocytic infiltrates in the lamina propria and/or submucosa. Consistent with the intestinal lesions, there were high incidences of watery faeces in both treated groups and body weight loss (high dose group only). The intestinal effects were probably attributable to ipilimumab, since similar effects (inflammatory colitis) were seen in Cynomolgus monkeys treated with ipilimumab alone.

Other findings were increased lymphoid follicles, expansion of the marginal zone in the red pulp and germinal centre hypocellularity in the spleen; lymphoid hypocellularity of the thymus; acinar cell degranulation in the pancreas; interstitial mononuclear cell infiltrates and tubular degeneration/regeneration in kidneys, portal mononuclear cell infiltrates in the liver (lower albumin globulin ratio was also seen); and myeloid hypercellularity in the bone marrow. While some of the histological changes in spleen, thymus, pancreas, kidneys and liver may be related to the pharmacological/immunological effects of nivolumab and/or ipilimumab, in the absence of data on the effects of individual drug component in the same study, it is difficult to assess whether the drug combination resulted in a new toxic effect (target organ toxicity was not seen in repeat dose toxicity studies conducted with nivolumab alone or in earlier studies conducted with ipilimumab). T lymphocyte counts (total T lymphocyte, T helper lymphocytes [CD4+] and T cytotoxic lymphocytes [CD8+] and B lymphocytes) and WBC were increased in the treated groups (mainly males) in the combination study and were probably pharmacological effects of both nivolumab and ipilimumab. The T cell dependent antibody response (TDAR) determined by serum levels of anti KLH IgM and anti KLH IgG was also increased in the treated groups, reflecting the pharmacological activities of nivolumab and/or ipilimumab. Anti-KLH responses were not determined in the nivolumab toxicity studies, but the same effects were seen in studies with ipilimumab.

Overall, signs of toxicity were mainly related to the extension of pharmacological effects arising from PD-1 blockade. Histological changes appearing to be indicative of organ toxicity were seen in the study conducted with the combination of nivolumab and ipilimumab. Since the combination study did not investigate the toxicity of individual components, it is difficult to come to a conclusion whether nivolumab in combination with ipilimumab could result in any unique toxicity not seen with either drug alone.

ADAs were often detected in monkeys, but the exposures were not markedly affected after weekly or twice weekly dosing for one to three months in most animals.

Genotoxicity

No genotoxic studies have been conducted, in accordance with TGA adopted guideline for biotechnology derived products.[14] As a high molecular weight protein, nivolumab is not expected to interact directly with DNA or other chromosomal materials.

Carcinogenicity

No carcinogenicity studies were conducted, in accordance with TGA adopted guidelines.[15]

[14] European Medicines Agency, "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)", June 2011.
[15] European Medicines Agency, "ICH Topic S 9 Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008)", December 2008; European Medicines Agency, "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)", June 2011.

Reproductive and developmental toxicity

In a prenatal and postnatal development study in Cynomolgus monkeys, nivolumab (0, 10, 50 mg/kg twice weekly IV from the period of organogenesis until delivery or pregnancy loss) caused a dose dependent increase in pregnancy (in the 3rd trimester) or infant loss (within the first month). Pregnancy loss was also increased in the 1st trimester in the high dose group. The number of pregnancy loss in the 1st trimester (3/16, 18.75%, excluding one loss due to umbilical thrombus, which was probably not related to drug treatment) was higher than the concurrent control (2/16, 12.5%) as well as the historical controls (36/467, 7.7%; range 0-16.7%) and hence a treatment relationship cannot be excluded. Other parameters in dams or infants (including blood lymphocyte phenotyping, immunoglobulin, anti nuclear antibodies, and TDAR) were unremarkable.

Toxicokinetic data after delivery showed that exposure was generally maintained in maternal animals through postpartum Day 91 (PD 91) and gradually declined (very low levels on PD 182: ~7 µg/mL). The serum levels in infants were comparable to maternal animals (70% or higher up to PD 91; below the level of detection on PD 182). The exposures in pregnant monkeys ($AUC_{0\text{-}168h}$ 117,000 and 541,000 µg.h/mL at 10 and 50 mg/kg, respectively) were 8 and 35 times, respectively, the clinical exposure based on AUC.

ADA was detected in 22% of the treated mothers although the presence of circulating nivolumab probably inhibited the detection of ADA in other dams. Except for one low dose monkey, the presence of ADA did not appear to affect nivolumab exposure.

The observed effects in the study in monkeys are consistent with reports in the literature. PD-1 pathway has been identified as playing a fundamental role in maintaining immune tolerance to the foetal allograft. The PD-L1 molecule is expressed at the uteroplacental interface and protects the concepti from maternal T cell mediated immunity.[16] Blockade of PD-L1 signalling in mice has been shown to abolish fetomaternal tolerance, resulting in increased foetal resorption and abortion.[17] In a murine model of allogeneic pregnancy (CBA x B6 strains mated), maternal treatment with an anti PD-L1 antibody (doses administered from shortly after implantation up to approximately halfway through the period of organogenesis) increased the incidence of foetal resorption from a spontaneous rate of 18% to 86%.[18] In further experiments involving pregnant B cell deficient mice (conducted to confirm the role of T cells in mediating these effects), blockade of the PD-1 pathway by an anti PD-L1 antibody caused foetal rejection in 100% of animals. Based on the above, nivolumab can be reasonably expected to cause embryofoetal loss in pregnant patients.

Pregnancy classification

The sponsor has proposed Pregnancy Category C.[19] Given the extreme nature of the adverse effects predicted based on the mechanism of action and the findings in the

[16] Guleria I, et al. A critical role for the programmed death ligand 1 in fetomaternal tolerance. *J Exp Med.* 202: 231-237 (2005).
[17] Guleria I, et al. A critical role for the programmed death ligand 1 in fetomaternal tolerance. *J Exp Med.* 202: 231-237 (2005); Wafula PO, et al. PD-1 but not CTLA-4 blockage abrogates the protective effect of regulatory T cells in a pregnancy murine model. *Am J Reprod Immunol.* 62: 283-292 (2009).
[18] Guleria I, et al. A critical role for the programmed death ligand 1 in fetomaternal tolerance. *J Exp Med.* 202: 231-237 (2005).
[19] Category C: "Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details."

monkey study (that is, abortion and embryofoetal lethality), Pregnancy Category D[20] is considered appropriate.

Immunotoxicity

In an immunotoxicology study in Cynomolgus monkeys dosed with nivolumab and challenged with 3 different antigens (hepatitis B surface antigen, 2,4-dinitryphenyl-Ficoll or humuan melanoma SKMel cells) once monthly for 3 months, nivolumab elicited only a modest increase in humoral responses to SKMel (compared to anti CTLA4 antibodies and vehicle controls) and no response to hepatitis B surface antigen or 2,4-dinitryphenyl (DNP)-Ficoll. Nivolumab (and ipilimumab) decreased naïve T cells (CD4+) (no effects on Treg subsets or CD8+ subsets) but increased CD4+ effector memory cells, consistent with the findings in the 3 month repeat dose toxicity study (discussed above). With regard to effects on humoral responses, results different from the monkeys treated with nivolumab were reported in a study in PD-1 deficient mice, which mounted a significantly increased IgG3 (IgG1 and IgM unaffected) response to the antigen, DNP-Ficoll, compared with the wild type littermates.[21]

A study in PD-1 knockout mice showed increased infiltrating immune cells and anti-ovalbumin antibodies in the bronchoalveolar fluid (BALF) following an ovalbumin challenge compared with the wild type littermates. Several pro-inflammatory chemokines and cytokine mRNA (including IFNγ and IL1a) were also upregulated in lung tissues in the PD-1 knockout mice. The findings suggest that PD-1 blockade might increase respiratory sensitisation. Histological examination of lung tissues showed no difference (including inflammatory cell infiltration) between PD-1 knockout and wild type mice. Nivolumab is expected to increase the potential of autoimmunity and the development of sensitisation to some products.

In mouse models of lymphocytic choriomeningitis virus (LCMV) infection, the absence of PD-1 pathway signalling resulted in fatal CD8+ T cell mediated pathology due to killing of virally infected endothelial cells resulting in cardiovascular collapse,[22] suggesting that administratiton of nivolumab to patients with viral infections may result in stronger immune reactions and increased toxicity compared to uninfected patients. PD-1 deficient mice also had decreased survival associated with uncontrolled bacterial proliferation and inflammatory response in the lung to M. tuberculosis infection, compared with wild type animals.[23] Similar results were observed in PD-1 deficient mice infected with murine hepatitis virus (increased fibrinogen like protein 2, tissue damage and mortality compared with the wild type littermates).[24] PD-1 deficient mice developed autoimmune dilated cardiomyopathy as a result of the development of auto antibodies to troponin I.

[20] Category D: "Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details."
[21] Nishimura H, et al. Immunological studies on PD-1 deficient mice: implication of PD-1 as a negative regulator for B cell responses. *Int Immunol.* 10: 1563-72 (1998).
[22] Frebel H, et al. Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. *J. Exp. Med.* 209: 2485-2499 (2012); Mueller SN, et al. PD-L1 has distinct functions in hematopoietic and nonhematopoietic cells in regulating T cell responses during chronic infection in mice. *J. Clin. Invest.* 120: 2508-2515 (2010).
[23] Lazar-Molnar E, et al. Programmed death-1 (PD-1)–deficient mice are extraordinarily sensitive to tuberculosis. *PNAS* 107: 13402-13407 (2010).
[24] Chen Y, et al. Programmed death (PD)-1-deficient mice are extremely sensitive to murine hepatitis uirus strain-3 (MHV-3) infection. *PLoS Pathogens* 7: e1001347 (2011).

Paediatric use

Nivolumab is not recommended for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

Summary

- The submission contained an adequate set of studies investigating pharmacology, PK and toxicity. The scope of nonclinical studies was in accordance with TGA adopted ICH guidelines applicable to biotechnology derived pharmaceuticals and to anticancer pharmaceuticals. All pivotal toxicity studies were GLP compliant.
- In vitro studies established that nivolumab binds to human PD-1 with nanomolar affinity, is able to block the binding of the PD-1 receptor's endogenous ligands (PD-L1 and PD-L2), and enhances T-cell immune responses. Nivolumab binds to Cynomolgus monkey PD-1, but not to mice, rat or rabbit PD-1. Nivolumab does not recognise related molecules such as CD28, CTLA-4, inducible T-cell co-stimulator (ICOS), or B and T lymphocyte attenuator (BTLA). In vivo studies conducted in mice with a surrogate anti PD-1 antibody (4H2), showed significant anti-tumour activity for the drug in some models but not in other models (including a melanoma model). Coupled with evidence of the PD-1 pathway being usurped by melanomas (to overcome active T cell immune surveillance), the submitted pharmacology studies offer some support for efficacy in the treatment of cancer. However, a mouse model of melanoma showed no efficacy with the anti-mouse PD-1 antibody (4H2). There were no studies in animal models on the efficacy of nivolumab in combination with ipilimumab.
- Safety pharmacology was limited to a single dose toxicity study in Cynomolgus monkeys mainly to assess cardiovascular changes. In this study, there were no treatment-related changes after a single administration of nivolumab. Toxicity studies showed no evidence of CNS, cardiovascular or respiratory effects.
- Pharmacokinetic studies showed small volume of distribution and slow clearance with elimination t1/2 5-11 days in monkeys. There was no significant difference between males and females. After repeated administration, there was no accumulation in the 1 month combination study of nivolumab administered with ipilimumab, but accumulation was generally evident in other studies with nivolumab. There were no studies on metabolism or excretion. Being a protein, nivolumab is expected to be degraded to small peptides and amino acids, and eliminated. The protein nature also suggests that nivolumab is not expected to cause or be subject to pharmacokinetic drug-drug interactions.
- In a single dose toxicity study in Cynomolgus monkeys, there were no treatment-related effects on clinical signs, body weight or clinical chemistry after IV administration of nivolumab up to 10 mg/kg. Higher doses (50 mg/kg IV twice weekly) were also well tolerated in repeat dose studies (see below).
- Repeat dose toxicity studies included a 1 and 3 month study in Cynomolgus monkeys. Clinical pathology or histological examination did not reveal any specific target organ toxicity for nivolumab. In both studies, a diffuse pattern of mild to slight inflammatory infiltration was seen in many organs/tissues, which were also present in control animals generally at a lower incidence. This effect may be related to PD-1 blockade. Increased blood CD4+ and CD8+ effector memory T cells (CD28-CD95+), as well as blood and spleen CD8+ central memory T cells (CD28+CD95+) were detected in the treated groups, consistent with the pharmacological action of nivolumab. ADAs were

detected in some treated monkeys, but the exposures were generally not markedly affected.

- A 4 week combination study was conducted in Cynomolgus monkeys to explore the effect of combining nivolumab with ipilimumab. The study did not include groups treated with nivolumab or ipilimumab alone, and hence it is difficult to assess whether the combination resulted in any new toxic effect. Findings in animals treated with the combination included inflammatory changes in the intestines (and watery faeces and body weight loss) and lesions in a number of organs (kidneys, liver, spleen, bone marrow, thymus). Some of findings were probably related to the pharmacological/immunological effects of nivolumab and/or ipilimumab. Increased T cell dependent antibody response was also observed, reflecting the pharmacological activities of nivolumab and/or ipilimumab.
- Genotoxicity and carcinogenicity studies were not conducted, which is considered acceptable.
- In a reproductive toxicity study (treatment starting from the period of organogenesis until delivery or pregnancy loss) in monkeys caused a dose dependent increase in pregnancy and infant loss consistent with the effect of PD-1 blockade. Pregnancy Category D is recommended.
- Findings in PD-1 knockout mice suggest increased immune reactions and autoimmunity in patients from the blockade of the PD-1 pathway.

Conclusions

- The proposed mechanism of action was demonstrated in nonclinical studies. Anti-tumour activity was observed in animal tumour models for some tumours but not others (including a murine melanoma model).
- Toxicity studies with nivolumab alone did not identify specific target organ toxicity. Mild to slight inflammatory cell infiltration was seen in multiple organs, and increased blood and spleen CD4+ and/or CD8+ effector/central memory T cells, consistent with the pharmacological action of nivolumab. A 4 week combination study with nivolumab and ipilimumab showed inflammatory changes in the intestines and lesions in other tissues, and increased T-cell dependent antibody response. The findings in the toxicity studies with nivolumab and in PD-1 knockout mice suggest enhanced immunity and potential for the development of autoimmunity in patients.
- A pre/postnatal study in monkeys showed increased in pregnancy and infant loss, consistent with the effect of PD-1 blockade. Pregnancy Category D is recommended.
- There are no nonclinical objections to the registration of Opdivo for the proposed indication provided efficacy was demonstrated in clinical studies and autoimmunity is manageable.

IV. Clinical findings: melanoma

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

Introduction

There were three separate clinical evaluation reports, as follows:

- for melanoma:
  - the main CER ("MEL"); and
  - a supplementary report ("suppl. CER") for Study 067 (this also updated the clinical evaluator's recommendations in melanoma)
- for squamous cell NSCLC:
  - one report ("SQ NSCLC CER")

Clinical rationale

Nivolumab is a monoclonal antibody that inhibits the PD-1 receptor (also known as CD279), which is expressed on activated T-lymphocytes. Similar to the CTLA-4 receptor, stimulation of PD-1 results in an inhibitory effect on T-cell function. The normal function of the PD-1 receptor is to limit or "check" overstimulation of immune responses. There are two known normal ligands for PD-1: PD-L1 (also known as CD274 or B7-H1) and PD-L2 (also known as CD273 or B7-DC). Multiple normal tissues express PD-L1, whereas PD-L2 is expressed only in macrophages and dendritic cells.[25]

Several different tumours, including melanoma, express PD-L1.[26] Tumour expression of PD-L1 may result in inhibition of T-cell mediated antitumour effects. The clinical rationale for PD-1 receptor blockade with nivolumab is to remove such inhibition.

Guidance

The following EMA guidelines, which have been adopted by the TGA, are considered relevant to the current submission:

- Guideline on the evaluation of anticancer medicinal products;[27]
- Guideline on the clinical investigation of PK of therapeutic proteins;[28]
- Guideline on the clinical evaluation of QT interval prolongation.[29]

Compliance with these guidelines is considered in the relevant sections of this report.

[25] Dolan DE and Gupta S. PD-1 Pathway Inhibitors: Changing the Landscape of Cancer Immunotherapy. *Cancer Control* 21: 231-237 (2014).
[26] McDermott DF and Atkins MB. PD-1 as a potential target in cancer therapy. *Cancer Medicine* 2: 662-673 (2013).
[27] European Medicines Agency, "Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4)", 13 December 2012.
[28] European Medicines Agency, "Guideline on the clinical investigation of pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)", 24 January 2007.
[29] European Medicines Agency, "Note for Guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (CHMP/ICH/2/04)", November 2005.

Contents of the clinical dossier

The submission contained the following clinical information:

- Two Phase I dose escalation studies of nivolumab monotherapy (MDX-1106-01 and MDX-1106-03).
- One Phase 1 dose escalation study of nivolumab in combination with ipilimumab (CA209004).
- Two pivotal Phase III efficacy/safety studies of nivolumab monotherapy (CA209066 and CA209037);
- One pivotal Phase II efficacy/safety study of nivolumab in combination with ipilimumab (CA209069);
- One Phase II study of nivolumab monotherapy in subjects with non-small cell lung cancer, which provided safety data (CA209063);
- One Phase II study of nivolumab monotherapy in subjects with renal cell carcinoma, which provided data on safety and QT prolongation (CA209010);
- 3 population pharmacokinetic analyses, which included some exposure-response analyses.
- Literature references.

Paediatric data

The submission did not include paediatric data. All the submitted clinical studies excluded subjects aged less than 18 years. The sponsor has a Paediatric Investigation Plan agreed with the EMA. The first report of a study conducted as part of the plan is due in October 2017. The sponsor also has a Paediatric Plan agreed with the FDA in the United States, with the first results being due in the 2nd quarter of 2018.

Good clinical practice

All study reports in the submission included an assurance that the study was conducted in accordance with Good Clinical Practice (GCP), as defined by the ICH.

Pharmacokinetics

Studies providing pharmacokinetic data

There were only two studies in the submission in which intensive PK sampling was conducted. In Study MDX-1106-01, intensive sampling was conducted after a single dose of nivolumab. In Study MDX-1106-03 (CA209003), intensive sampling was conducted after single and multiple dosing. In the remainder of the studies in the submission, only sparse PK sampling was conducted and these data were analysed in population PK analyses. All the submitted studies were conducted in subjects with advanced cancer.

Three separate population PK analyses were included in the submission. The first (dated 26 May 2014) focussed on subjects with NSCLC. The second analysis (dated 18 July 2014) included all the data from the first analysis as well as data from one other study and it focussed on subjects with advanced melanoma. The third analysis (dated 8 December 2014) included all the data from the first and second analyses, as well as a further two studies of the combination of ipilimumab and nivolumab. It also focussed on subjects with advanced melanoma. Only the second and third analyses are reviewed in this report.

Table 4 shows the studies relating to each pharmacokinetic topic.

Table 4. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in patients with advanced cancer	General PK Single dose	MDX-1106-01	*
	Single & multi-dose	MDX-1106-03	*
Population PK analyses	Melanoma subjects	-	
	Melanoma subjects – combination with ipilimumab	-	

* Indicates the primary aim of the study.

None of the PK studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

The submitted data indicate that the PK of nivolumab are consistent with the PK of endogenous IgG4, with a low volume of distribution, slow clearance and a half- life of approximately 3-4 weeks. The PK data included in the submission are considered to meet the requirements of the relevant EMA guideline adopted by the TGA.[30] Overall, the PK data are considered acceptable.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 5 shows the studies relating to each pharmacodynamic (PD) topic.

Table 5. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on serum cytokines	MDX-1106-01
		MDX-1106-03
	Effect on lymphocyte populations	MDX-1106-01
		MDX-1106-03
	Receptor occupancy	MDX-1106-03
Secondary Pharmacology	Effect on QT interval	CA209010

[30] European Medicines Agency, "Guideline on the clinical investigation of pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)", 24 January 2007.

None of the PD studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

Only a limited amount of clinical PD data was included in the submission. The studies were acceptable.

Dosage selection for the pivotal studies

For monotherapy, the selected dose of 3 mg/kg every 2 weeks was based on both preclinical and clinical data. The clinical data came from Study MDX-1106-03. In this dose ranging study, objective responses were observed 31.4%, 41.2% and 20.0% of melanoma patients treated at 1, 3 and 10 mg/kg, respectively. No maximum tolerated dose was determined.

For combination therapy, the chosen doses for nivolumab and ipilimumab were based on the findings of a Phase I dose escalation study (CA209004). This study is discussed.

Efficacy

Nivolumab monotherapy

Studies providing efficacy data

Study CA209066 was a Phase III, randomised, double blind, double dummy trial with two parallel groups. Subjects with advanced melanoma were randomised to receive either nivolumab or dacarbazine.

The primary objective of the trial was to compare the clinical benefit (as measured by the duration of overall survival [OS]) provided by nivolumab, compared to that provided by dacarbazine, in subjects with previously untreated, unresectable or metastatic melanoma.

The secondary objectives were:

- To compare the duration of investigator assessed PFS of nivolumab versus dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma;
- To compare the investigator assessed objective response rate (ORR) of nivolumab versus dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma;
- To evaluate whether programmed cell death ligand 1 (PD-L1) expression is a predictive biomarker for OS;
- To evaluate health-related quality of life (HRQoL) as assessed by European Organisation for Research and Treatment of Care (EORTC) QLQ-C30 (Quality of Life Questionnaire - Core 30).

A number of exploratory objectives were also stated.

The trial was conducted 76 sites in 16 countries (Argentina, Australia, Canada, Chile, Denmark, Finland, France, Germany, Greece, Israel, Italy, Mexico, Norway, Poland, Spain, and Sweden). These were countries where dacarbazine was considered first line standard of care for patients with previously untreated, unresectable or metastatic melanoma.

The study commenced in January 2013 and was closed on 24 June 2014.[31] The date of data cut-off for the study report was 5 August 2014 and the report itself was dated 20 October 2014. The study has been published.[32]

Study CA209037 was a Phase III, randomised, open trial with two parallel groups. Subjects with advanced melanoma, who had progressed on prior anti CTLA-4 therapy, were randomised (2:1) to receive either nivolumab or the investigator's choice of chemotherapy (either dacarbazine or the combination of carboplatin with paclitaxel).

The primary objective of the study was to estimate the ORR in nivolumab treatment group and to compare OS of nivolumab to investigator's choice in subjects with advanced melanoma.

The secondary objectives were to:

- Compare the PFS of nivolumab to investigator's choice in subjects with advanced melanoma.
- Evaluate whether PD-L1 expression is a predictive biomarker for ORR and OS.
- Evaluate HRQoL as assessed by the EORTC QLQ-C30.

There were also a number of exploratory objectives relating to safety, PK, immunogenicity, potential biomarkers for response, the effects of genetic variation on clinical endpoints and QoL.

The study was conducted at 90 centres in 14 countries (USA, Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland and the United Kingdom).

The study commenced in December 2012 and is ongoing. The study report included in the submission was an *interim* study report. The cut-off date for inclusion of imaging data in the report was 10 March 2014. The report itself was dated 18 July 2014. The study has been published.[33]

Study MDX-1106-01 was a Phase I trial that was the first-in-man study for nivolumab. Study MDX-1106-03 (CA209003) was a Phase I study in subjects with various types of advanced/recurrent malignancies. The study included 107 subjects with advanced melanoma and these were treated with doses ranging from 0.1 to 10 mg/mg every 2 weeks for up to 96 weeks.

Evaluator's conclusions on efficacy for monotherapy

There were two Phase III studies submitted to support use of nivolumab as monotherapy in patients with advanced melanoma. Study CA209066 examined use of the drug in first-line treatment, whereas study CA209037 examined use in subjects who had progressed on ipilimumab and (if BRAF mutation positive) a BRAF inhibitor.

Study CA209066 was well designed and executed. The design of the study complied with the requirements of the relevant EMA guideline adopted by the TGA.[34] The study demonstrated a highly clinically significant efficacy benefit when compared to dacarbazine, with a 58% reduction in the risk of death. The survival benefit did not appear to be associated with any deterioration in quality of life. The evidence for the efficacy of

[31] The sponsor states this study is still ongoing and is scheduled to be operationally closed in May 2019.
[32] Robert C, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* 372: 320-30 (2015).
[33] Weber J, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncology* 16: 375-384 (2015).
[34] European Medicines Agency, "Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4)", 13 December 2012.

nivolumab monotherapy in the first line treatment of advanced melanoma is therefore convincing.

Only interim results were available for Study CA209037. They demonstrated that nivolumab monotherapy is associated with an overall response rate of 31.7%. Although not subjected to statistical analysis, this response rate was numerically higher than that obtained with dacarbazine or paclitaxel/carboplatin (10.6%). The study has not yet demonstrated a benefit for nivolumab compared to chemotherapy in terms of clinically meaningful endpoints such as OS, PFS, or quality of life. Data from the first planned (interim) analysis of OS should be sought from the sponsor. However, the population studied in this trial had already failed ipilimumab and a BRAF inhibitor (if BRAF mutation positive). Such subjects have limited treatment options available. The ORR of 31.7% was notably numerically higher than that obtained with chemotherapy (10.6%). Given the limited treatment options available, the submitted evidence of efficacy is considered sufficient to support approval of nivolumab monotherapy in subjects who have progressed following treatment with ipilimumab and a BRAF inhibitor (if BRAF mutation positive).

The data from these monotherapy studies suggest that nivolumab produces higher response rates in subjects who have PD-L1 positive tumours. However, the OS data from Study CA209066 suggest that the drug is also effective in subjects with PD-L1 negative tumours, with survival being greater in these subjects with nivolumab than with dacarbazine. The data therefore do not support limiting approval to subjects with PD-L1 positive tumours. There was no analysis of tumour PD-L2 expression as a potential biomarker for efficacy.

Among subjects who develop progressive disease while on nivolumab, a proportion (approximately 25%) will develop or maintain evidence of a response if treatment is continued. However it is not clear whether these subjects derive any clinical benefit (for example, improved survival) from continued treatment. These data therefore do not support persisting with nivolumab treatment after disease progression.

Nivolumab in combination with ipilimumab

Studies providing efficacy data

Study CA209069 was a Phase II, randomised, double blind with two parallel groups. Subjects with previously untreated advanced melanoma were randomised to receive either nivolumab in combination with ipilimumab or ipilimumab monotherapy.

The primary objective of the study was to compare the ORR, as determined by investigators, of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with BRAF wild type unresectable or metastatic melanoma. Secondary objectives were to:

- Compare PFS with nivolumab combined with ipilimumab to that with ipilimumab monotherapy in subjects with BRAF wild type unresectable or metastatic melanoma;
- Evaluate ORR and PFS of nivolumab combined with ipilimumab and ipilimumab monotherapy in BRAF mutation positive subjects with unresectable or metastatic melanoma;
- Evaluate Health Related Quality of Life (HRQoL) as assessed by the EORTC QLQ-C30.

There were also a number of exploratory objectives relating to safety, assessment of OS, PK, immunogenicity, potential biomarkers for response, the effects of genetic variation on clinical endpoints and QoL.

The study was conducted at 21 centres in 2 countries (19 in the United States and 2 in France).

The trial commenced in August 2013 and is ongoing. The cut-off date for data for inclusion in the study report was 24 July 2014. The report itself was dated 5 December 2014. The study has been published.[35]

Study CA209004 was a Phase Ib, open label dose escalation trial of nivolumab in combination with ipilimumab. The primary objective was to assess safety and tolerability of the combination. One of the secondary objectives was to assess preliminary evidence of efficacy for the combination. The study was conducted between December 2009 and June 2014 at 4 centres in the US. The study report was dated December 2014.

Evaluator's conclusions on efficacy for combination therapy

There was one pivotal study submitted to support the combination of nivolumab with ipilimumab (CA209069). It was conducted in the first line setting. The study was well designed and executed. However, it was a Phase II trial that used ORR as the primary endpoint. Although an impressive response rate was obtained with the combination (59.7% in the BRAF wild type population), the data on duration of response were not mature and therefore it has not been established that these responses are durable.

The relevant EMA guideline adopted by the TGA[36] does not consider ORR to be an acceptable primary endpoint for a confirmatory study, and suggests that clinically relevant endpoints such as PFS or OS should be used. Investigator assessed PFS was a secondary endpoint in this trial and a significant benefit was demonstrated. Median PFS was prolonged by approximately 4 months (8.87 versus 4.73 months).

The choice of comparator (ipilimumab) in the study was appropriate. However, it would be useful to know whether the combination provides any benefit over nivolumab monotherapy. Cross trial comparison of efficacy results in the BRAF wild type population in the first line setting suggests that this may be the case, as shown in Table 6.

Table 6. Cross-trial comparison of monotherapy and combination therapy for ORR and median PFS.

	Study	ORR	Median PFS
Nivolumab monotherapy	CA209066	40.0 %	5.06 m
Combination therapy	CA209069	59.7%	8.87 m

However, cross trial comparisons are unreliable. It is noted that the sponsor is currently undertaking another Phase III trial in the first line setting (Study CA209067) with three treatment arms: nivolumab monotherapy, ipilimumab monotherapy, and combination therapy. The co-primary endpoints for this study are OS and PFS. Given the limitations of Study CA209069, it may be prudent to await the results of Study CA209067 before approving combination treatment.

Although the pivotal study was conducted in the first line setting and included BRAF mutation positive subjects, the combination was not compared to a standard first line therapy for these subjects (that is, BRAF inhibitor therapy). The study therefore does not support the use of the combination in the first line treatment of BRAF mutation positive disease.

In the Phase I study the ORR with the proposed combination regimen was lower than in the pivotal study (44% versus 59.7%).

[35] Postow MA, et al. Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma. *N Engl J Med.* 372: 2006-17 (2015).
[36] European Medicines Agency, "Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4)", 13 December 2012.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

There were three studies in the submission that are considered pivotal: Studies CA209037 and CA209066 for monotherapy, and Study CA209069 for combination therapy. In these studies, the following safety data were collected:

- General adverse events (AEs) were assessed either continuously or at each study visit;
- The sponsor identified the following as AEs of special interest: endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis and rash. These were referred to in the dossier as 'select AEs'. The choice of these events was based on observations in early studies and the expected effects of an immunotherapy. Because multiple individual AE terms could be used to describe these toxicities, the following categories of AEs were examined: endocrine, gastrointestinal, hepatic, pulmonary, renal and skin. Hypersensitivity/infusion reactions were added as another category of select AEs.
- Measurement of vital signs and physical examination were conducted at baseline and at regular intervals during treatment.
- Laboratory tests were performed at baseline, at regular intervals during treatment and during follow up. Testing included complete blood count with differential, liver function testing, urea, creatinine, calcium, magnesium, sodium, potassium, chloride, lactate dehydrogenase, glucose and thyroid function testing. Study CA209069 also included monitoring of amylase and lipase.

Non-pivotal efficacy studies

The following non-pivotal efficacy studies provided safety data:

- Studies MDX-1106-01 and MDX-1106-03 (CA209003), which were Phase I dose ranging studies conducted using nivolumab monotherapy in subjects with various advanced malignancies;
- Study CA209004, which was a Phase I dose ranging study of the combination of nivolumab with ipilimumab in subjects with advanced melanoma;
- Study CA209010, which was a Phase II dose ranging study in subjects with renal cell carcinoma;
- Study CA209063, which was a Phase II single arm study in 117 subjects with advanced NSCLC.

Safety monitoring in the non-pivotal studies was generally similar to that used in the pivotal studies. Electrocardiograms (ECGs) were monitored in some of the early studies.

None of the non-pivotal studies had a placebo or active comparator arm. Hence the most informative safety data are likely to come from the pivotal studies.

Patient exposure

Approximately 1130 subjects had received treatment with nivolumab monotherapy. Only 188 subjects had been treated with the combination of nivolumab and ipilimumab. The submission did not contain an analysis of overall extent of exposure by dose and duration.

Safety issues with the potential for major regulatory impact

Liver toxicity

As described above, nivolumab treatment is associated with hepatic toxicity, manifested mainly as elevated liver function tests (LFTs). From the individual study reports, it appears that no cases of severe drug induced liver injury (DILI) have been documented. It also appears that there have been no patients who meet Hy's law criteria predictive of severe DILI in the submitted studies. However, one subject in an ongoing study (CA209067) developed DILI, although it was not clear whether the subject had received nivolumab. The sponsor should be asked whether any cases of severe DILI or subjects meeting Hy's law criteria have been reported from any clinical trials or in the post-marketing setting.

Haematological toxicity

Nivolumab appears to be associated with lymphopaenia. Other haematological toxicities were uncommon. Overall, haematological toxicity occurs less frequently with nivolumab than with chemotherapy regimens used in the two pivotal monotherapy studies.

Serious skin reactions

Skin toxicity is very common with nivolumab therapy. However most events are mild or moderate in severity, with grade 3 or 4 toxicity occurring in less than 5% of subjects. No cases of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) were reported in the submitted studies. There appear to have been at least two reports of toxic epidermal necrolysis in ongoing studies (CA209012 and CA209067) but it is not clear from the submitted information whether these subjects were receiving nivolumab. The sponsor should be asked whether any cases of SJS or TEN have been reported from any clinical trials or in the post-marketing setting.

Cardiovascular safety

In comparative studies nivolumab did not appear to be associated with an increased of cardiovascular AEs. In a Phase II study, the drug was not associated with prolongation of the QT interval.

Unwanted immunological events

Nivolumab is associated with a variety of autoimmune toxicities. Such toxicities are expected given the mechanism of action of the drug and their occurrence with other checkpoint inhibitors such as ipilimumab and pembrolizumab. The most commonly reported events were skin disorders, colitis/diarrhoea, pneumonitis, hepatitis (elevated LFTs) and disorders of the thyroid. Other reported events included uveitis, hypophysitis, Guillain-Barre syndrome and pancreatitis.

In the pivotal studies, the median time to onset for the various categories of 'select' AEs was generally less than 10 weeks. However, in some patients onset was delayed. For example, time to onset of endocrine AEs in Study CA209066 ranged up to 59.9 weeks.

In the pivotal studies investigators were provided with guidelines for the management of these events. The most common treatment was systemic corticosteroids. For skin events topical corticosteroids were the most commonly used agents. Most events resolved with use of these agents and withholding of nivolumab.

Post marketing data

Two spontaneous adverse reaction reports had been received in Japan, where the drug was approved in July 2014. One was for disease progression and one was for an infusion reaction.

Evaluator's conclusions on safety

Monotherapy

The safety profile of nivolumab monotherapy has been reasonably well characterised. The submission included data on approximately 1,100 subjects and median duration of treatment with nivolumab in the two pivotal studies was approximately 6 months.

The overall toxicity profile of nivolumab monotherapy was comparable to, or slightly better than, that observed for the conventional chemotherapy agents used as comparators (dacarbazine and paclitaxel/carboplatin), with generally lower incidences of grade 3/4 AEs, serious AEs (SAEs), and discontinuations due to AEs. In the two pivotal studies there were no deaths related to nivolumab treatment. The rate of discontinuation of nivolumab due to AEs in the two pivotal studies was reasonably low (6.8% and 9.3%, respectively), suggesting that toxicities produced by the drug are manageable.

The most prominent toxicities associated with nivolumab were those assessed as autoimmune in nature. Pneumonitis caused a number of deaths in early studies, although not in the pivotal melanoma trials. Overall, the incidence of grade 3/4 or serious autoimmune AEs was low in the pivotal trials.

Nivolumab is intended for use in a population of subjects with severe disease with limited life expectancy. The safety profile of the drug described above is not so adverse as to preclude its use in such a population. The drug as monotherapy is therefore considered to have acceptable safety given the intended patient population.

Combination therapy

The experience with nivolumab in combination with ipilimumab is limited, with safety data from only 188 subjects. The median duration of treatment with the combination in the pivotal study was only 2.15 months.

The combination was associated with significant increases in overall toxicity compared to ipilimumab alone in the pivotal study. Grade 3/4 AEs (69.1% versus 43.5%), serious AEs (61.7% versus 39.1%) and discontinuations due to AEs (42.6% versus 10.9%) were all increased in the combination arm. There were also two deaths in the combination arm that were assessed as related to the combination, compared to none in the ipilimumab arm. One additional death was assessed as related to the combination in study CA209004.

The pattern of excess AEs in the combination arm of the pivotal study was consistent with that observed for nivolumab monotherapy, predominantly autoimmune type events.

A cross trial comparison of rates of grade 3/4 AEs, SAEs and discontinuations due to AEs is shown in Table 7.

Table 7. Cross trial comparison of rates of grade 3/4 AEs, SAEs and discontinuations due to AEs.

	Study	Grade 3/4	SAE	Discontinuation
Nivolumab monotherapy	CA209066	34.0 %	31.1 %	6.8 %
	CA209037	34.3 %	44.0 %	9.3 %
Combination therapy	CA209069	69.1 %	61.7 %	42.6 %

These data suggest that combination therapy may be associated with significantly greater toxicity than nivolumab monotherapy. The high rate of discontinuation due to AEs with

combination treatment is a concern. If the combination regimen were to be approved, there would need to be convincing evidence of an efficacy benefit over nivolumab monotherapy.

First round benefit-risk assessment

First round assessment of benefits

The benefits of **nivolumab monotherapy** in the treatment of advanced melanoma are:

- Improved OS (compared to dacarbazine) in the first line setting with a 58% reduction in the risk of death. The proportion of subjects still alive at 12 months was increased from 42.1% to 72.9%.
- A substantial rate of tumour response (31.7%) in subjects who had already failed ipilimumab and a BRAF inhibitor (if BRAF mutation positive). Such subjects have limited treatment options available.

The benefits of **nivolumab in combination with ipilimumab** in the treatment of advanced melanoma are:

- A substantial rate of tumour response (59.7%) in previously untreated subjects. This response rate was significantly higher than that achieved with ipilimumab monotherapy (10.8%). However, data on duration of response were not mature.
- An increase in PFS compared to ipilimumab monotherapy in previously untreated subjects, with a 60% reduction in the risk of a PFS event. Median PFS was prolonged by approximately 4 months.

In the current submission there were no studies that compared nivolumab monotherapy with the combination of nivolumab and ipilimumab. Cross trial comparison suggests that there may be some additional efficacy benefit from use of the combination.

The efficacy of nivolumab (as monotherapy or in combination) has not been compared with that of BRAF inhibitor therapy in subjects with BRAF mutation positive disease.

First round assessment of risks

The risks of nivolumab in the treatment of advanced melanoma are:

- An increased risk (compared to conventional chemotherapy) of a variety of autoimmune type events such as pneumonitis, endocrinopathies, hepatitis, colitis, skin disorders etc.

As monotherapy, the overall toxicity of nivolumab is comparable to, or slightly lower than, that of conventional chemotherapy.

The toxicity of the combination of nivolumab with ipilimumab is significantly greater than that of ipilimumab monotherapy. In the current submission there were no studies that compared the safety of nivolumab monotherapy with that of the combination of nivolumab and ipilimumab. Cross trial comparison suggests that the combination may be associated with significantly more toxicity.

First round assessment of benefit-risk balance

The benefit-risk balance of **nivolumab monotherapy**, given the proposed usage, is favourable. The drug has better efficacy and comparable or better safety than conventional chemotherapy.

It is considered that the currently available data are insufficient to permit a conclusion that the **combination of nivolumab with ipilimumab** has a favourable benefit-risk balance in the treatment of advanced melanoma. Limitations of the data are as follows:

- The pivotal data to support the efficacy of the combination come from a phase II study (CA209069) that used ORR as the primary efficacy endpoint. The relevant EMA guideline adopted by the TGA does not support use of ORR as a primary efficacy endpoint.
- Data on duration of response in CA209069 were not mature, and it could not be concluded that the observed responses were durable.
- The number of subjects treated with combination therapy was low (approximately 180 in all). Median duration of treatment in CA209069 was short (2.15 months). This raises a concern that the toxicity of combination treatment has not been adequately defined.
- The combination was associated with a significant increase in toxicity compared to ipilimumab monotherapy. Cross trial comparisons suggest that the combination may also be associated with a significant increase in toxicity compared to nivolumab monotherapy.

Given these limitations, it would be difficult to justify commencing a patient with advanced melanoma on combination therapy rather than nivolumab monotherapy. It is noted that the sponsor is currently conducting a further Phase III trial (CA209067) that compares three treatments: nivolumab monotherapy, ipilimumab monotherapy, and the combination of ipilimumab with nivolumab. OS will be a primary endpoint. It is recommended that the results of this study be evaluated prior to a decision being made to approve combination therapy.

For both monotherapy and combination therapy, the submitted data do not establish a role for nivolumab in the first line treatment of subjects with BRAF mutation positive disease.

First round recommendation regarding authorisation

It is recommended that the application be approved for a more limited indication than that proposed by the sponsor, along the following lines:

> *Opdivo, **as monotherapy**, is indicated for the treatment of patients with unresectable or metastatic melanoma. **In subjects with BRAF V600 mutation positive disease, treatment should be commenced only after failure of BRAF inhibitor therapy**.*

Clinical questions

Efficacy

1. The sponsor to provide a summary of the first planned interim analysis of OS from Study CA209037.
2. The sponsor to provide a summary of any updated data on duration of response from Study CA209069.
3. The sponsor to advise when the results of Study CA209067 will be available.

Safety

4. In the submitted study reports, nivolumab treatment was associated with hepatic toxicity. However, no cases of severe DILI were reported. In addition it appears that there were no cases of subjects meeting 'Hy's law' criteria predictive for severe DILI. There appears to have been at least one case of DILI in one of the ongoing studies (CA209067). It was not clear whether this subject had received nivolumab. Please advise whether any cases of severe DILI or subjects meeting Hy's law criteria have been reported with nivolumab treatment in clinical trials or in the post-market setting.
5. In the submitted study reports, no cases of SJS or TEN appear to have been reported. However, there appear to have been at least two reports of TEN in ongoing studies (CA209012 and CA209067). It was not clear whether these subjects had received nivolumab. Please advise whether any cases of SJS or TEN have been reported with nivolumab treatment in clinical trials or in the post market setting.
6. The submitted study reports did not provide analyses of several of the clinical chemistry parameters that were monitored during the trials (urea, calcium, magnesium, sodium, potassium, chloride, glucose). Please comment.

Second round evaluation

Responses to questions

(Q1) Overall survival in Study CA209037

The sponsor submitted an updated 'ad hoc' study report for study CA209037. The cut-off date for inclusion of data in the report was 12 November 2014. The previous report had a cut-off of 10 March 2014. The report itself was dated 5 February 2015 (previous report was dated 18 July 2014).

At the time of the updated analysis 182/405 randomised subjects (45%) had died. Nivolumab treatment was not associated with any survival benefit when compared with investigator's choice of chemotherapy.

The sponsor argued that failure to demonstrate a survival benefit could have been due to the following reasons:

- Survival data were not yet mature. The final survival analysis is planned after 260 deaths have occurred (expected in late 2015);
- There were some imbalances in prognostic factors at baseline such as history of brain metastases (19.5% of nivolumab subjects versus 13.5% of chemotherapy subjects) and presence of elevated LDH (51.1% versus 34.6%) that may have adversely affected outcomes in the nivolumab arm. The estimated OS rate of 76.7% at 6 months for nivolumab treated subjects in this study was somewhat lower than the observed 6 month survival rates for nivolumab treated melanoma subjects in both MDX-1106-03 (82%) and CA209066 (84.1%);
- OS in the chemotherapy arm was prolonged (median = 13.67 months) compared with historical data. In the sample size calculation for the trial it was assumed that median OS in the chemotherapy group would be only 8 months;
- More subjects in the chemotherapy arm received further anticancer treatment after disease progression (63.2% versus 41.5%). Subjects in the chemotherapy arm who developed progressive disease were not permitted to cross over to nivolumab therapy. However, 31.6% of these subjects did receive an anti PD-1 agent (mainly

pembrolizumab) after disease progression. This may have confounded the analysis of survival.

An updated descriptive analysis of PFS (as assessed by the investigators) was also conducted.

> *Comment: OS was a co-primary endpoint in this study and is a more clinically relevant endpoint than overall response rate, the other co-primary endpoint. The survival data are approaching maturity and there is no suggestion of a beneficial effect of nivolumab. This raises the question of whether nivolumab monotherapy should have a role in the treatment of subjects who have already progressed after ipilimumab ± a BRAF inhibitor. The descriptive data on PFS suggest there may be a beneficial effect on this endpoint, and the frequent use of subsequent anti PD-1 therapy in the chemotherapy arm may have confounded the survival results. It is noted that there was a late separation of the PFS curves. The final survival analysis should be reviewed when available, to see whether a similar effect is observed for OS. In addition, the updated report did not include any results for quality of life endpoint. These data should also be provided when available.*
>
> *Given the potential confounding of the survival data, this reviewer still considers it would be reasonable to approve nivolumab monotherapy for 2nd/3rd line use.*

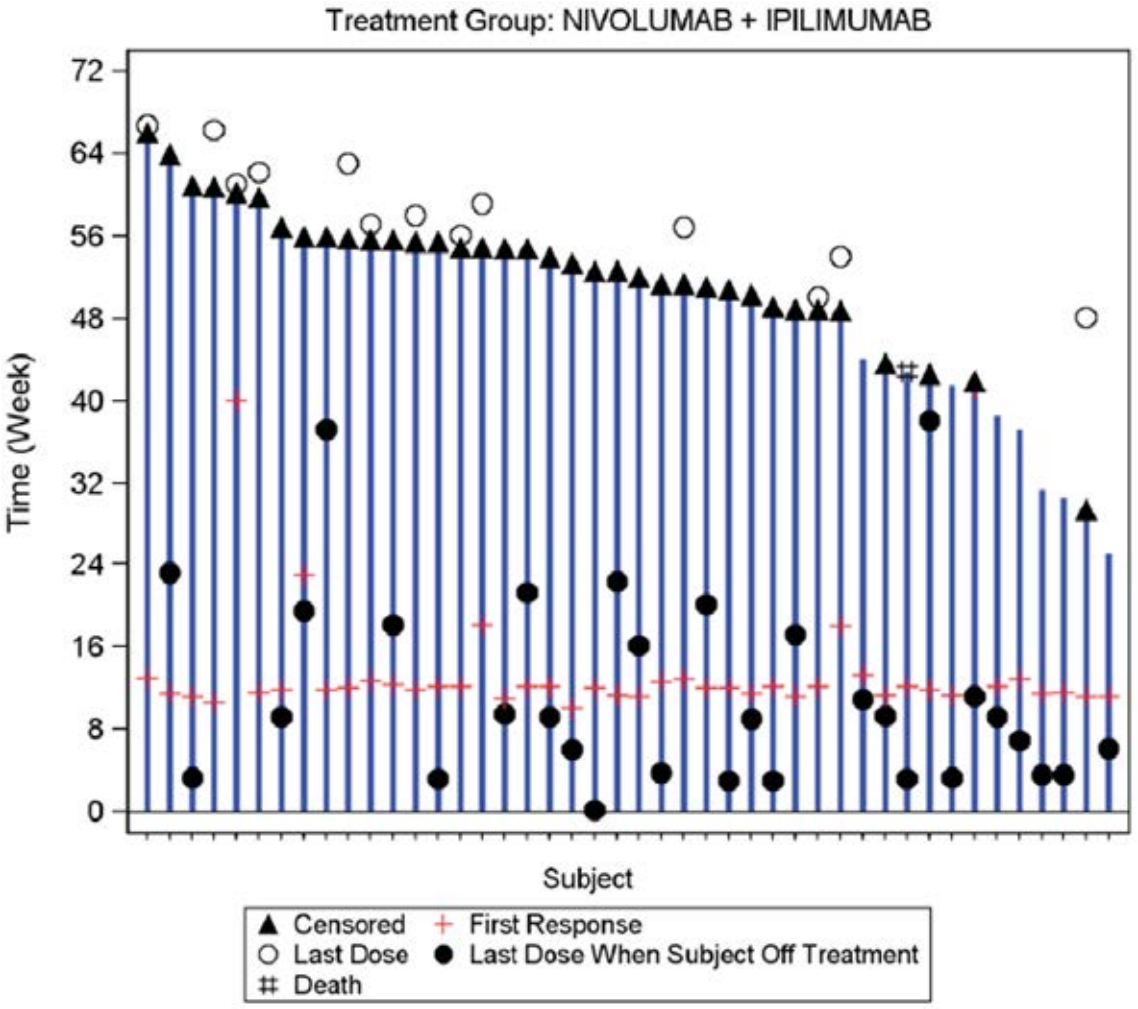
(Q2) Duration of response in Study CA209069

The sponsor provided an addendum to the original study report, which contained updated data on efficacy and safety. The cut-off date for data for inclusion in the study report was 30 January 2015 (cut-off for the original report was 24 July 2014). The addendum was dated 4 May 2015 (original report was dated 5 December 2014).

The ORR in the BRAF wild type population was 61.1% (44/72) in the combination arm compared to 10.8 % (4/37) in the ipilimumab arm. The difference was statistically significant ($p < 0.0001$). Results in the all randomised population were again similar (58.9% versus 10.6%; $p < 0.0001$). In the combination arm 22.2% of subjects achieved a complete response, compared to none in the ipilimumab arm.

Median duration of response had still not been reached in either arm. Figure 3 illustrates the features of the 44 responses observed in the combination arm in the BRAF wild type population. Responses were still ongoing in 36/44 subjects. Typically, responses occurred at around week 12 and were still ongoing at around week 52, suggesting that responses are generally durable.

Figure 3. Study CA209069 – Time to response and duration of response (updated data).



Bar indicates PFS. Response and progression as assessed per Investigator.
Vertical axis origin corresponds to randomization date.
PFS was measured from randomization to last tumor assessment (if no progression, no subsequent therapy, and no death) and scan frequency was at Week 12 than then every 6 weeks for the first year. Nivolumab+ipilimumab doses were administered Q3W for 4 doses and then nivolumab was administered Q2W; therefore, the last dose (open circle) may have occurred after the last tumor assessment.

The addendum also included updated analyses of PFS and OS. The results of these analyses were consistent with those contained in the original study report.

(Q3) Results of Study CA209067

The sponsor indicated that the results of this study are now available. The study has recently been published.[37] It is understood that a clinical study report will be submitted to the TGA and will be the subject of a separate evaluation report.

(Q4) Drug induced liver injury

The sponsor presented the results of an updated review of 10 clinical studies it had conducted. A total of 2,354 subjects had received nivolumab in these studies.

Among nivolumab treated subjects there was only one case that met the criteria for Hy's law (concurrent elevation of a transaminase > 3x upper limit of normal (ULN) and total

[37] Larkin J, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med.* 373: 23-34 (2015).

bilirubin 2x ULN, with alkaline phosphatase < 2x ULN and no other identifiable cause). This was a subject enrolled in Study CA209069 who received the combination of nivolumab with ipilimumab. The patient developed abnormal LFTs/grade 4 hepatitis on Day 164 of the study, 86 days after his last nivolumab infusion. Nivolumab was discontinued and he was treated with prednisone. The hepatitis resolved.

The sponsor therefore estimated the incidence of cases meeting Hy's law criteria by to be 1 in 2,354 (0.04%). A review of post marketing data did not identify any further cases meeting Hy's law criteria, or any cases of severe DILI.

> *Comment: These data suggest that nivolumab may be associated with rare cases of severe DILI. Given the life-threatening nature of advanced melanoma, this finding does not significantly alter the overall benefit-risk balance for the drug.*

(Q5) SJS/TEN

The sponsor conducted a search of its safety database for reports of SJS or TEN up to 22 April 2015. No cases of SJS were reported. Two reports of TEN were identified. Both of these cases were fatal. The first case involved a subject with advanced NSCLC treated with nivolumab and ipilimumab in a Phase I study. The diagnosis of TEN was established on biopsy. The second case involved a subject with melanoma treated with nivolumab monotherapy in a named patient program. An initial skin biopsy suggested erythema multiforme. Nivolumab was discontinued and she was treated with immunosuppressive therapy. The rash resolved. The patient subsequently commenced treatment with ipilimumab and the rash returned. A diagnosis of TEN was made and the patient died soon afterwards.

> *Comment: Severe/life threatening dermatological adverse events appear to occur with nivolumab but are rare. This finding is not considered to significantly alter the overall benefit-risk balance for the drug. However, the product information should warn that fatal dermatological reactions, such as TEN, have been observed with nivolumab.*

(Q6) Clinical chemistry results

The sponsor presented a summary of the incidence of worsening of the following parameters: calcium, potassium, magnesium and sodium for the three pivotal studies. In terms of new grade 3 or 4 abnormalities, the incidence of hyponatraemia was increased with nivolumab in two of the three studies (Table 8).

Table 8. Incidence of new grade 3 or 4 hyponatraemia.

Study	Nivolumab arm	Comparator arm
CA209066 (monotherapy)	3.1%	3.3%
CA209037 (monotherapy)	5.1%	1.1%
CA209066 (combination therapy)	8.5%	2.2%

There were no other consistent findings relating to these parameters across the three studies. The sponsor stated that monitoring of chloride was not required in the studies. It appears that urea and glucose were also not routinely monitored.

Other issues

Use in subjects with BRAF mutation positive disease

Earlier, it was recommended that the indication be restricted such that, for patients with BRAF mutation positive disease, therapy with a BRAF inhibitor should have been tried and failed in the first instance. The reasons for this recommendation were:

- In Study CA209066, subjects with BRAF mutation positive disease were excluded;
- In Study CA209037, subjects with BRAF mutation positive disease could only be enrolled if they had failed BRAF inhibitor therapy;
- None of the studies had compared nivolumab with a BRAF inhibitor in subjects with BRAF mutation positive disease.

The sponsor has presented a series of arguments against the recommended restriction:

- Immunotherapies such as nivolumab have a mechanism of action that is independent of the presence or absence of a BRAF mutation;
- Nivolumab treatment produces similar response rates in both BRAF mutation positive and mutation negative disease;
- Although BRAF inhibitors have been shown to produce a high response rate in patients with BRAF mutation positive disease, the duration of such responses is usually short. Responses with nivolumab are durable;
- Expert opinion, such as the NCCN guideline,[38] recommends nivolumab or pembrolizumab as an option for the first line treatment of BRAF mutation positive disease;
- The EMA expert advisory committee has recommended approval of nivolumab, without a restriction relating to BRAF mutation status;
- The TGA has recently approved pembrolizumab with an indication that includes first-line treatment of BRAF mutation positive patients. According to the information contained in the approved product information, a comparative study comparing pembrolizumab with a BRAF inhibitor appears not to have been conducted.

  Comment: BRAF inhibitors are established therapy for the first-line treatment of advanced melanoma positive for a BRAF V600 mutation. In the experience of this reviewer, regulatory approval of a new agent for this indication would normally require a head-to-head comparison (that is, a Phase III trial of the new agent versus an approved BRAF inhibitor in subjects with BRAF mutation positive disease). However, if the TGA has waived this requirement for pembrolizumab, it would appear reasonable to do the same for nivolumab.

Safety of combination therapy

As indicated above, the sponsor provided updated safety data from study of combination therapy (CA209069). The pattern of AEs was consistent with that described in the original clinical study report (CSR). There was a small increase in the proportion of subjects who experienced drug related AEs and SAEs as shown in Table 9. With the longer follow-up there was a notable increase in the proportion of subjects who had discontinued treatment due to drug related AEs: from 36.2% in the original CSR to 55.3% in the CSR addendum.

[38] National Comprehensive Cancer Network (NCCN), NCCN Clinical Practice Guidelines in Oncology – Melanoma, Version 3.2015. 2015.

Table 9. Incidence of new grade 3 or 4 hyponatraemia.

	Incidence (%) Combination (n = 94) versus Ipilimumab (n = 46)	
	Original CSR	**CSR Addendum**
Minimum follow-up	6 months	11 months
Drug-related AEs	**91.5%** versus 91.3%	**91.5%** versus 93.5%
Drug-related AEs – grade 3 or 4	**51.1%** versus 19.6%	**54.3%** versus 23.9%
Drug-related serious AEs	**47.9%** versus 19.6%	**53.2%** versus 28.3%
Discontinuations due to drug-related AEs	**36.2%** versus 8.7%	**55.3%** versus 21.7%

Although a high proportion of subjects discontinued from the combination due to AEs, the sponsor states that 71.1% of subjects who discontinued treatment due to study drug toxicity had obtained a confirmed objective response.

There was one additional death in the combination arm that was considered related to treatment. This was a subject who died due to panhypopituitarism with severe cortisol deficiency and adrenal crisis. Therefore, in total there were 3 drug related deaths in the combination arm and none in the ipilimumab arm.

Second round benefit-risk assessment

The additional information provided is not considered to significantly alter the benefit-risk assessment made in the first round.

Second round recommendation regarding authorisation

It is recommended that the application be approved for monotherapy. Although the data are considered inadequate to support regulatory approval for first line treatment in subjects with BRAF mutation positive disease, it may be appropriate to grant such an approval to be consistent with pembrolizumab.

Approval for combination therapy is not recommended until such time as the data from Study CA209067 have been evaluated.

V. Clinical findings: melanoma (supplementary)

Introduction

This is a follow up submission to register a new chemical entity. The initial submission to register the product has been evaluated. The sponsor had sought approval for use of the product both as monotherapy and in combination with ipilimumab. Use as monotherapy was recommended for approval but it was recommended that approval for combination use be withheld until the results of an ongoing Phase III study (CA209-067) became available. The sponsor has now submitted a report of this study, which is the subject of this evaluation.

The sponsor has made an editorial change to the proposed indication, which now reads:

> *Opdivo, as monotherapy is indicated for the treatment of patients with unresectable or metastatic melanoma. Opdivo, in combination with Yervoy (ipilimumab), is indicated for the treatment of patients with unresectable or metastatic melanoma.*

Scope of the clinical dossier

The supplementary submission contained the following clinical information:

- A full clinical study report for Study CA209067;
- An addendum to the clinical study report, providing data additional analyses according to baseline tumour PD-L1 status;
- A revised draft PI and Consumer Medicines Information (CMI) document.

Paediatric data

There have been no changes since the original evaluation.

Good clinical practice

The submitted study report for Study CA209067 contained an assurance that the trial was conducted in accordance with GCP, as defined by the ICH.

Pharmacokinetics

No new PK data were submitted.

Pharmacodynamics

No new PD data were submitted.

Dosage selection for the pivotal studies

The dosage regimens for nivolumab monotherapy and combination therapy that were used in Study CA209067 were the same as those justified and used in the previously evaluated studies.

Efficacy

Studies providing efficacy data

Study CA209067 was a Phase III randomised, double blind trial with three parallel groups. The study had three phases: screening, treatment, and follow up.

The **primary objective** was to compare PFS and OS of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma.

Secondary objectives were to:

- Compare ORR of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with unresectable or metastatic melanoma;

- Evaluate differences in OS, PFS, and ORR between nivolumab combined with ipilimumab and nivolumab monotherapy;
- Evaluate whether PD-L1 expression is a predictive biomarker for OS;
- Evaluate HRQoL as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.

There were also a number of exploratory objectives related to assessing duration of response, time to response, safety, PK, immunogenicity, biomarkers and HRQoL.

The study is being conducted at 137 sites in 21 countries (Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Spain, Sweden, Switzerland, United Kingdom, and United States).

The trial commenced in June 2013 and is ongoing. The study report presented is an interim study report, with a cut-off date for inclusion of data of 17 February 2015. The report itself was dated 19 June 2015. The study has been published.[39]

Evaluator's conclusions on efficacy

Study CA209067 was well designed and executed. The design complied with the relevant EMA guidelines adopted by the TGA.

The study provided further clinical evidence to support the use of nivolumab as **monotherapy** in the treatment of advanced melanoma. Previously evaluated data (CA209066) had shown that nivolumab, as first line treatment, was associated with a highly clinically significant efficacy benefit when compared to dacarbazine, with a 58% reduction in the risk of death. Study CA209067 has now demonstrated that the drug is superior to ipilimumab in the first line treatment of melanoma. The new study also provided evidence of efficacy in the first line treatment of subjects with BRAF mutation positive disease.

The study also demonstrated that the **combination** of nivolumab and ipilimumab was superior to ipilimumab alone. It therefore confirmed the findings of the previously evaluated Phase II study (CA209069). The efficacy results with the combination (Hazard Ratio [HR] for PFS, median PFS, ORR) were less impressive in the Phase III study than in the Phase II study, but this was also true of ipilimumab.

Study CA209067 was not designed to establish superiority of combination treatment over nivolumab monotherapy. The hypothesis that combination therapy is superior to nivolumab monotherapy has therefore not been formally tested. However the efficacy results obtained with the combination were numerically superior to those obtained with monotherapy. When comparing the two treatments, the HR for PFS was 0.74 and the 95% CI did not include 1.00 (0.60 to 0.92). Median PFS was longer (11.50 versus 6.87 months) and response rate was higher (57.6% versus 43.7%).

Subgroup analyses suggested that the combination might be more effective than nivolumab monotherapy in subjects with PD-L1 negative tumours. However, the study was not powered to detect such an effect. It is noted that the sponsor is not proposing to limit the indication for combination treatment to subjects with PD-L1 negative tumours. It is also not clear whether the validated PD-L1 assay is to be marketed in Australia.

Overall, it is concluded that the efficacy of nivolumab monotherapy has been adequately demonstrated, and that combination treatment has been demonstrated to be superior to ipilimumab monotherapy. However, doubts remain as to whether combination therapy is superior to nivolumab monotherapy.

[39] Larkin J, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med.* 373: 23-34 (2015).

Safety

Studies providing safety data

The only additional safety data submitted were those generated by study CA209067. In this study the following safety data were collected:

- General AEs were assessed by continuously. Toxicities were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
- The following categories of AEs (referred to as 'select AEs') were of special interest: endocrine, gastrointestinal, hepatic, pulmonary, renal, skin and hypersensitivity/infusion reactions.
- Physical examination including measurement of vital signs was conducted on Day 1 of Weeks 1, 3, 4 and 5 during cycles 1 and 2, and then on Day 1 of Weeks 1, 3 and 5 for subsequent cycles.
- Laboratory tests were performed on Day 1 of Weeks 1 and 4 during cycles 1 and 2, and then on Day 1 of Weeks 1 and 5 for subsequent cycles. Tests performed were: complete blood count with differential, LFTs, urea, creatinine, calcium, magnesium, sodium, potassium, chloride, lactate dehydrogenase (LDH), glucose, amylase, lipase and thyroid function tests.

Patient exposure

A total of 313 subjects received treatment with nivolumab monotherapy, 313 with combination treatment and 311 with ipilimumab.

- In the nivolumab monotherapy arm the median number of doses of nivolumab received was 15.0 (range 1-38). Median duration of treatment was 6.6 months (95% CI: 5.16 to 9.69);
- In the combination arm the median number of doses of nivolumab received was 4.0 (range 1-39) and the median number of doses of ipilimumab received was 4.0 (range 1-4). Median duration of treatment was 2.8 months (95% CI: 2.40 to 3.91);
- In the ipilimumab monotherapy arm the median number of doses of ipilimumab received was 4.0 (range 1-4). Median duration of treatment was 3.0 months (95% CI: 2.56 to 3.91).

  Comment: Duration of nivolumab treatment was notably reduced in the combination arm compared to the nivolumab monotherapy arm. This is likely to be due to increased toxicity with combination treatment as discussed below.

Safety issues with the potential for major regulatory impact

Liver toxicity

Study CA209067 demonstrated again that nivolumab is associated with hepatotoxicity. However, there were no cases of severe DILI or cases that met Hy's law criteria.

Haematological toxicity

In the nivolumab arm there was one case neutropaenia resulting in sepsis and death. The investigator assessed the event as being related to the drug. However, laboratory monitoring did not suggest that nivolumab was associated with increased haematological toxicity compared with ipilimumab. Neutropaenia was not identified as a toxicity associated with nivolumab in the previously evaluated studies.

Serious skin reactions

As noted previously, nivolumab is associated with serious skin reactions. In CA209067, serious skin select AEs occurred in approximately 1% of subjects in each of the three treatment arms. There was only one case of TEN and this occurred in a subject in the ipilimumab monotherapy arm. There were no cases of SJS.

Cardiovascular safety

The incidence of overall cardiac AEs was not increased with nivolumab compared to ipilimumab (6.1% with nivolumab, 10.5% with the combination, 11.6% with ipilimumab). The incidence of overall vascular AEs was comparable across the study arms (17.9% with nivolumab, 17.6% with the combination, 17.0% with ipilimumab).

Unwanted immunological events

The incidence of hypersensitivity/infusion reaction select AEs was increased with nivolumab compared to ipilimumab (5.1% with nivolumab, 4.5% with the combination, 2.9% with ipilimumab). However, grade 3 or 4 events only occurred in 1 subject in the nivolumab arm and 1 subject in the ipilimumab arm.

Post marketing data

No post marketing data were submitted.

Evaluator's conclusions on safety

Study CA209067 provides additional data to define the safety profile of **nivolumab monotherapy**. These data indicate that nivolumab has a favourable overall safety profile when compared to that of ipilimumab. Nivolumab was associated with a lower incidence of grade 3 or 4 AEs (43.5% versus 55.6%), serious AEs (36.1% versus 52.1%) and AEs leading to discontinuation (13.7% versus 22.5%). This is despite duration of treatment being longer in the nivolumab arm. The two drugs have a similar spectrum of toxicities, with autoimmune type events (for example, diarrhoea/colitis, skin toxicity, hepatotoxicity, endocrinopathies) being prominent.

The study confirms that **combination therapy** is associated with significant additional toxicity when compared to either nivolumab monotherapy or ipilimumab monotherapy. When compared to nivolumab monotherapy, combination treatment is associated with an increase incidence of grade 3 or 4 AEs (68.7% versus 43.5%), serious AEs (69.3% versus 36.1%) and AEs leading to discontinuation (43.1% versus 13.7%). The increase in toxicity is due to a higher incidence of autoimmune type events. In the previously evaluated phase II study of combination therapy, there was an increased incidence of treatment-related deaths in the combination arm. However, this was not noted in CA209067.

First round benefit-risk assessment

First round assessment of benefits

Considering the previously evaluated studies together with the results of CA209067, the benefits of **nivolumab monotherapy** in the treatment of advanced melanoma are:

- Improved OS (compared to dacarbazine) in the first line setting with a 58% reduction in the risk of death. The proportion of subjects still alive at 12 months was increased from 42.1% to 72.9%.

- Improved PFS (compared to ipilimumab) in the first line setting with a 43% reduction in the risk of a PFS event. The proportion of subjects still alive and free of progression after 9 months was increased from 29% to 52%.
- A substantial rate of tumour response (31.7%) in subjects who had already failed ipilimumab and a BRAF inhibitor (if BRAF mutation positive). Such subjects have limited treatment options available.

Based on the results of CA209067, the benefits of **nivolumab in combination with ipilimumab** in the treatment of advanced melanoma are:

- An increase in PFS compared to ipilimumab monotherapy in previously untreated subjects, with a 58% reduction in the risk of a PFS event. Median PFS was prolonged by approximately 8.6 months.

Study CA209067 suggested that combination therapy might also be associated with superior efficacy compared to nivolumab monotherapy. However, the study was not designed to formally test this comparison

First round assessment of risks

Considering the previously evaluated studies together with the results of CA209067, the risks of nivolumab in the treatment of advanced melanoma are:

- An increased risk of a variety of autoimmune type events such as pneumonitis, endocrinopathies, hepatitis, colitis, skin disorders, etcetera

As monotherapy, the overall toxicity of nivolumab is comparable to, or slightly lower than, that of conventional chemotherapy, and somewhat lower than that of ipilimumab.

The toxicity of the combination of nivolumab with ipilimumab is significantly greater than that of ipilimumab monotherapy or nivolumab monotherapy.

First round assessment of benefit-risk balance

The benefit-risk balance of **nivolumab monotherapy**, given the proposed usage, is favourable. The drug has better efficacy and comparable or better safety than conventional chemotherapy or ipilimumab.

Given that nivolumab monotherapy has better efficacy and safety than ipilimumab, it should be preferred over ipilimumab for the treatment of advanced melanoma. Regulatory approval for **combination therapy** should only be considered if the combination has a more favourable benefit-risk balance than nivolumab alone. A statistically significant improvement in efficacy for combination treatment over nivolumab monotherapy has not been established, as Study CA209067 was not designed to demonstrate this. However the study clearly demonstrates that the combination is associated with a significant increase in toxicity. It is therefore not possible to conclude that combination treatment is associated with a more favourable benefit-risk balance than nivolumab monotherapy.

If approval is restricted to nivolumab monotherapy, ipilimumab could still be used as a second line agent. It is possible that such sequential use of these agents might result in comparable efficacy and reduced toxicity compared to combination use. However, there are no clinical data to support such a hypothesis.

First round recommendation regarding authorisation

It is recommended that the application for **monotherapy** should be approved. The proposed monotherapy indication is acceptable. It is recommended that the application

for use in combination with ipilimumab be rejected due to uncertain evidence of efficacy, and concerns regarding increased toxicity, when compared to nivolumab monotherapy.

Clinical questions

Efficacy

1. The sponsor to provide an assurance the formulation of nivolumab used was identical to that being proposed for registration in Australia.
2. In Study CA209067, the subgroup analysis of PFS according to baseline PD-L1 status suggested that combination therapy might be superior to nivolumab monotherapy in subjects with PD-L1 negative tumours. The sponsor to advise whether the validated PD-L1 IHC assay used to classify subjects in this analysis will be marketed in Australia.

VI. Clinical findings: SQ NSCLC

Introduction

This clinical evaluation report is of data in support of use in squamous non-small cell lung cancer (SQ NSCLC) and is supplementary to the melanoma clinical evaluation report.

The sponsor's submission to register nivolumab, dated 6 January 2015, requested approval for use in advanced melanoma. Based on the sponsor's summary of outcomes in a Phase III study in SQ NSCLC, the TGA allowed the scope of the submission to enlarge.

The proposed indications are:

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

For the SQ NSCLC indication, the dosage and route of administration are as follows:

> *The recommended dose of Opdivo 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.*
>
> *Opdivo infusion must not be administered as an intravenous push or bolus injection.*

For the monotherapy use of nivolumab in advanced melanoma, the dosage regimen is the same as for SQ NSCLC (that is, 3 mg/kg IV over 60 minutes every 2 weeks, while there is clinical benefit and while the treatment is tolerated).

Clinical rationale

The sponsor states that historically, patients with SQ NSCLC had worse outcomes and fewer acceptable treatment options than patients with NSQ NSCLC (this was used to explain the sponsor's approach of pursuing SQ and NSQ NSCLC indications separately).

Some therapies in NSCLC are not indicated in SQ NSCLC. Pemetrexed is only indicated in locally advanced or metastatic NSCLC "other than predominantly squamous cell histology". Bevacizumab's NSCLC indication is restricted to NSQ NSCLC. Likewise, afatinib's approval is restricted to use in NSQ disease.

Contents of the clinical dossier

The dossier in support of nivolumab's use in SQ NSCLC was a rolling submission, that is, different components arrived at the TGA at different times. It included three studies as shown in Table 10.

Table 10. Incidence of new grade 3 or 4 hyponatraemia.

ID	Status	Description	Comment
Study 017	Final CSR	Phase III, randomised, controlled trial versus docetaxel in patients failing first-line treatment	pivotal
Study 063	Final CSR; and Addendum 1	Phase II, single arm study in 3rd or subsequent line patients	supportive
Study 003	Final CSR; and Addendum 1	Phase I, single arm study in various malignancies including NSCLC	supportive

The dossier also included a **population PK analysis** (with an update incorporating Study 017).

The Dossier does **not** include substantial clinical data in support of use in **NSQ NSCLC** (although in Study 003, some patients had this condition). The sponsor has not, in this application, requested approval for use in NSQ NSCLC.

A separate Phase III trial, Study 057, is studying patients with NSQ NSCLC. The sponsor has announced that this trial, comparing nivolumab versus docetaxel in previously treated patients, was stopped early because a planned interim assessment found that the study had shown superior OS in the nivolumab arm.

The sponsor also mentioned two studies in untreated NSCLC patients: CA209012 and CA209026. These studies were not submitted for review and are apparently outside of the scope of this clinical dossier.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

In the clinical study reports for Studies 017, 063 and 003, it was stated that GCP was adhered to.

Pharmacokinetics

Studies providing pharmacokinetic data

In Study 003, there was intensive PK sampling; this study has been taken into account in the melanoma clinical evaluation report and its PK findings are not re-evaluated here.

The document 'Nivolumab population PK in patients with solid tumours and exposure-response analysis in patients with previously treated squamous non-small cell lung

cancer' (report dated 23 April 2015) takes into account two large studies in NSCLC and is considered below.

Evaluator's conclusions on PK

The PK of nivolumab have been characterised in sufficient detail, primarily by successive population PK analyses. Findings derived from exposure-response analyses should be considered exploratory, given the suggestion that there may be confounding (that is, that unmeasured covariates may be influencing outcomes such as OS and AEs).

There is no indication that the PK of nivolumab vary appreciably in patients with SQ NSCLC and patients with melanoma.

The sponsor took the view that the influence of covariates on PK was clinically irrelevant if the effect size was <20%. There is an indication within Study 003 of a steep exposure-response curve around the dose being proposed (that is, ORR was 3% in NSCLC patients treated at 1 mg/kg, but >20% at 3 mg/kg and 10 mg/kg doses). It should be noted that no such threshold was seen in melanoma. Also, the formal 'exposure-response' analyses within population PK reports did not detect any strong relationship between exposure and efficacy. Nevertheless, even if the 'threshold' suggested by Study 003 exists, a change of <20% in exposure due to a single variable is much smaller than a 3 fold decrease in dose, so the sponsor's approach is probably reasonable in this regard.

Anti PD-1 mAbs may cause autoimmune AEs. The general approach is to withhold treatment and trial corticosteroids, but other agents may be required if AEs persist. One medicine sometimes used for autoimmune disease is intravenous immunoglobulin. There are grounds to suspect that nivolumab's PK would be influenced by use of high doses of IVIG, since elevated total Ig levels may saturate FcRn and facilitate degradation of nivolumab.[40] The sponsor is invited to comment.

Pharmacodynamics

No new PD data have been considered in this evaluation report.

Dosage selection for the pivotal studies

Study 017's CSR notes the 3 mg/kg once every two weeks (Q2W) dose regimen was chosen based on an interim analysis (24 February 2012) of data from ~300 subjects in Study 003:

> *The probability of a tumour response tended to approach a plateau for trough concentrations produced by 3 mg/kg and 10 mg/kg administered Q2W.*

No maximum tolerated dose was identified.

Efficacy

Studies providing efficacy data

Study 017 was a Phase III, randomised, open label study of the efficacy of nivolumab in the treatment of adult patients with previously treated advanced or metastatic squamous cell non-small cell lung cancer, using docetaxel as a comparator.

[40] Wang W, et al. Monoclonal antibody pharmacokinetics and pharmacodynamics. *Clinical Pharmacology & Therapeutics* 84: 548-558 (2008).

The primary objective was to compare OS of nivolumab versus docetaxel.

Secondary objectives were: to compare, across arms, ORR and PFS; to evaluate whether PD-L1 is a predictive biomarker for OS, ORR or PFS; and to evaluate disease-related symptom improvement by 12 weeks.

Exploratory objectives were: to assess safety and tolerability; to characterise PK and explore exposure-response relationships; to characterise immunogenicity; and to assess overall health status using the EQ-5D Index and visual analogue scale.

Study CA209063 ("063") was a single-arm, open label, Phase II study of nivolumab in subjects with advanced or metastatic SQ NSCLC who had received at least two prior systemic regimens. One of these had to be platinum doublet based chemotherapy. Some details of inclusion criteria were similar to those in Study 017.

The sponsor justified the single arm design by noting that no approved/proven efficacious therapies exist for SQ NSCLC patients who have progressed after two chemotherapies.

The primary objective of the study was to assess the clinical activity of nivolumab, as measured by independent radiology review committee (IRC) assessed ORR.

Study MDX1106-03 (CA209003) ("003") was a Phase I, open label, dose escalation study of nivolumab in subjects with various advanced or recurrent malignancies.

Evaluator's conclusions on efficacy

There was only one pivotal study in the setting of SQ NSCLC, Study 017. Apart from being an open-label study, it was well designed. Lack of blinding does not have a direct impact on the primary endpoint of OS. Efficacy results in the comparator docetaxel arm were not good relative to recent studies. This may be because Study 017 only examined SQ NSCLC, which may have a worse prognosis than NSQ NSCLC. The randomisation process appeared valid and baseline prognostic factors were mostly balanced across arms. It is possible that despite randomisation, there was an imbalance in unmeasured baseline prognostic factors; but the modest imbalances that were apparent (for example, in ECOG performance status) in Study 017 seemed to favour better results for docetaxel (as suggested by the lower HR, 0.51, in the multivariate analysis of OS).

Study 063, despite being uncontrolled, provided some evidence of nivolumab's efficacy as third (or subsequent) line therapy in SQ NSCLC.

In my view, there is acceptable evidence that nivolumab monotherapy (3 mg/kg Q2W) has sufficient efficacy in the proposed indication.

The sponsor proposes use of nivolumab in lung cancer as per the following indication:

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

The term 'locally advanced' is open to interpretation. NSCLC has well established clinical staging criteria, based on TNM classification. Study 017 included patients with stage IIIB or stage IV disease. Consideration should be given to whether the indication should specify stage IIIB/stage IV disease. Use of the term 'locally advanced' is enshrined in the indications of various other TGA approved therapies for NSCLC; also, the nivolumab PI 'Clinical Trials' section can provide further information about the type of patient studied. On balance, the term 'locally advanced' is acceptable to this evaluator.

The wording "on or after prior chemotherapy" opens up the possibility that use could be in patients groups not well tested in the trial programme. For example, patients refractory to targeted therapies might be considered to have progressed on prior chemotherapy. On the whole, that wording is acceptable (given that further information is supplied in the Clinical Trials section of the PI about the type of SQ NSCLC patients that have been studied).

In the pivotal and supportive SQ NSCLC trials of nivolumab, use was as monotherapy. This should be reflected in the indication, since use in combination with other therapies may result in an unpredictably altered benefit-risk profile. A preferable wording of the indication is:

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

Safety

Studies providing safety data

Studies 017, 063 and 003 provided evaluable safety data. There was a pooled analysis of safety from studies 017 and 063, within the Clinical Overview Update.

> *Evaluator's comments: Only where this pooled analysis provides major new safety information, above and beyond that found in individual CSRs, is it referenced. The two studies revealed different rates of some AEs, for example, pneumonitis, so a pooled analysis risks losing information, e.g. if pneumonitis is more likely in more heavily pre-treated subjects.*
>
> *The latest version of the proposed nivolumab PI presents AEs in SQ NSCLC according to the pooled dataset from 017 and 063. Supporting data were provided in a 'Clinical Overview Update Attachment' dated 4 March 2015.*

In Study 017, AEs were analysed primarily for events reported up to 30 days after the last dose of study medication. A separate analysis considered AEs reported up to 100 days after the last dose of study medication.

Patient exposure

In Study 017, the primary population for safety analysis was all treated subjects (131 nivolumab subjects, all receiving 3 mg/kg Q2W, and 129 docetaxel subjects). In Study 063, there were 117 treated subjects, all receiving nivolumab 3 mg/kg Q2W. Thus, the pooled analysis of safety across these two studies drew from 248 subjects given nivolumab.

In Study 003, there were 54 SQ NSCLC subjects, of whom 18 received 3 mg/kg Q2W; and there were a further 74 NSQ NSCLC subjects.

Safety issues with the potential for major regulatory impact

Liver toxicity

There are strong grounds to suspect nivolumab may cause immune related/autoimmune hepatitis. However, in SQ NSCLC studies, there was not a strong signal that this occurs commonly or that when it occurs it is particularly severe or irreversible.

Haematological toxicity

Nivolumab does not appear to cause marked haematological toxicity, although it may cause occasionally significant peturbations in blood counts (for example absolute lymphocyte counts may fall).

Serious skin reactions

There are strong grounds to suspect nivolumab may cause immune related/autoimmune skin reactions. However, in SQ NSCLC studies, there was not a strong signal that this occurs commonly or that when it occurs it is severe or irreversible.

Cardiovascular safety

There was no signal in the SQ NSCLC studies that nivolumab causes cardiovascular toxicity. However, it is plausible that immune related AEs arising from nivolumab use may occur within the cardiovascular system. For example, there has been a case report of myocarditis with use of pembrolizumab.

Unwanted immunological events

Hypersensitivity

In the pivotal study, hypersensitivity reactions and infusion related AEs were reported in 0.8% (nivolumab) versus 2.3% (docetaxel). The nivolumab case was mild and did not result in discontinuation, but premedication with acetaminophen and diphenhydramine was given for subsequent doses.

In Study 063, 94% of patients (110/117) received all doses of nivolumab without an IV infusion interruption. In 3/7 subjects, the reason for interruption was hypersensitivity.

Immunogenicity

In Study 017, n = 109 nivolumab subjects had evaluable anti-drug antibody tests at baseline and on treatment. 21 subjects were ADA positive, including 1/21 considered persistently positive, 3/21 with neutralising ADAs at least at one time point, and 4/21 with positive results as of the last test.

There were no hypersensitivity or infusion related AEs in subjects with ADAs.

There was no evidence of loss of efficacy in subjects with ADAs. Indeed, the three subjects with neutralising ADAs had relatively good OS (13.3, 19.2+ and 9.5 months).

In Study 063, 12/101 subjects (11.9%) had detectable ADA at any stage; in no subjects were ADAs persistently positive, and in no subjects were ADAs neutralising.

In Study 003, ADAs were detected in 8.6% after treatment started, and in 2 subjects across all tumour cohorts, ADAs were persistently positive (these 2 subjects had no unusual AEs).

The sponsor provided a pooled analysis of immunogenicity in the Clinical Overview Update for NSCLC. Data from Studies 017, 063, 037 and 066 were pooled, that is, the analysis included patients with SQ NSCLC and patients with advanced melanoma. Of 497 patients treated with nivolumab 3 mg/kg Q2W and evaluable for the presence of ADAs, 51 patients (10.3%) had treatment emergent ADAs, but only 4 patients (0.8%) were persistently positive, and only n = 5 (1.0%) had neutralising antibodies. The sponsor found no association between ADAs and altered PK or toxicity.

> *Evaluator's comment: Despite nivolumab being a fully human mAb, there remains potential for the formation of clinically relevant ADAs. Immunogenicity may emerge with ongoing therapy.*
>
> *The Clinical Overview Update is silent on whether, in the pooled analysis of ADAs, there was any association detected between ADAs and altered efficacy. Can the sponsor provide analysis of this association?*
>
> *The proposed PI notes that in studies of combined nivolumab and ipilimumab, "the clearance of nivolumab increased by 42% in the presence of anti nivolumab antibodies". Can the sponsor justify why the effect of anti nivolumab antibodies with monotherapy as described in the population PK analysis dated 8 December 2014 (i.e. 22% higher CL) should not be reported? Can the sponsor comment on the apparent difference between reports with regard to the influence of ADAs on PK?*

Immune related AEs

General comments

Checkpoint blockade can induce autoimmune AEs. The sponsor identified the following AEs for further characterisation: diarrhoea/colitis; hepatitis; pneumonitis; nephritis/renal dysfunction; hypothyroidism/thyroiditis; hyperthyroidism; hypophysitis; diabetes mellitus; adrenal insufficiency; and rash.

> *Evaluator's comment: Autoimmunity can affect virtually any body system. For example, there was a report of myasthenia in a patient receiving nivolumab. However, the sponsor's list is appropriate to characterise the commoner autoimmune/immune related AEs due to nivolumab.*
>
> *Attribution as 'autoimmune' is often unclear. For example, there are many causes of hepatitis, one of which is autoimmune hepatitis. However, overall, characterisation of potentially immune mediated AEs was very good in the Study 017 CSR. Also, the CSR analysed AEs reported within 30 days (main analysis) but also within 100 days. Results in this clinical evaluation report reflect the main analysis, but there were no dramatic differences based on the 100 day 'extended follow-up' safety data, which is relevant for immune related AEs that could potentially have a relatively late onset.*

Immune related AEs can be mitigated by early, appropriate management, and guidelines were provided to investigators to assist in the identification and treatment of such AEs.

> *Evaluator's comment: The frequency of immune-related AEs reported in this study can be generalised only if similar recommendations are made to prescribers, e.g. via the PI or other educational approaches.*

Diarrhoea/colitis

Diarrhoea was reported as an AE in 16% (nivolumab) versus 26% (docetaxel). However, there were two cases of colitis for nivolumab (one was grade 3-4), none for docetaxel. There was an earlier onset of gastrointestinal AEs in many docetaxel subjects, relative to nivolumab subjects (for example, 3.8% of nivolumab subjects had reported such an AE within 2 week, versus 17.8% of docetaxel subjects). Median time to onset was 5.6 weeks for nivolumab, 1 week for docetaxel. The case of grade 3 colitis in the nivolumab arm started at week 91. In 77% of affected nivolumab subjects (17/22), the AE resolved (over a median of 1.6 weeks, although one patient had ongoing symptoms at 33.4 weeks). Two of 21 nivolumab subjects required prednisone treatment (one grade 3 colitis, one grade 2 diarrhoea). In 5 nivolumab subjects, diarrhoea was reported on 2-3 separate occasions, and in 1 subject diarrhoea was reported 4 or more times. The sponsor was asked to comment on when colonoscopy was indicated in this study.

Hepatitis

As reflected by deranged LFTs, hepatitis was reported in 2.3% (nivolumab) versus 4.7% (docetaxel). No subject on nivolumab was reported to have elevated bilirubin. No subject required immunosuppressive medication.

Pneumonitis

There was an imbalance in reporting of relevant pulmonary AEs (Table 11).

Table 11. Pulmonary AEs.

Preferred Term (%)	Nivolumab 3 mg/kg N = 131			Docetaxel N = 129		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	7 (5.3)	2 (1.5)	0	3 (2.3)	1 (0.8)	1 (0.8)
PNEUMONITIS	6 (4.6)	2 (1.5)	0	1 (0.8)	0	0
LUNG INFILTRATION	1 (0.8)	0	0	0	0	0
ACUTE RESPIRATORY FAILURE	0	0	0	1 (0.8)	1 (0.8)	0
INTERSTITIAL LUNG DISEASE	0	0	0	1 (0.8)	0	1 (0.8)

Pulmonary AEs were reported as early as 4 weeks after onset of treatment for nivolumab, but as late as 36 wks. Median time to onset was 21.1 weeks in the nivolumab patients. In 6/7 nivolumab subjects, the AE resolved (over a median of 6.4 weeks, though one subject had ongoing symptoms at 30 weeks). Six of 7 nivolumab subjects had systemic corticosteroids. Two of 7 nivolumab subjects reported no potential risk factors for pneumonitis.

> *Evaluator's comment: Early management (for example, before the AE progresses to become severe or life threatening) may mitigate nivolumab's toxicity. Pneumonitis was a leading cause of discontinuation in the nivolumab arm; 3/131 subjects discontinued due to that AE. Also, in 5/131 nivolumab subjects, treatment delay was attributed to pneumonitis.*
>
> *Data about median time to onset, etcetera, are not robust. For example, in the pooled analysis across studies 017 and 063, the median time to onset of pneumonitis was 11.6 weeks rather than the 21.1 weeks reported for Study 017. Pooling may be inappropriate in that more heavily pre-treated subjects may have an earlier onset, or because by the time 017 was being conducted, investigators were less likely to allow early symptoms to evolve unchecked.*
>
> *Did any patients who developed pneumonitis receive concurrent chest radiotherapy?*

In Study 063 (Addendum 1), all causality relevant pulmonary AEs were reported in 6.8%; pneumonitis contributed most events (it was reported in 5.1% of subjects; all cases were considered drug related, and 4 cases reached grade 3, although all cases resolved; 1 case was reported more than 30 days after last nivolumab dose; 1 case led to discontinuation; 1 case recurred with steroid taper and required mycophenolate).

Nephritis/renal dysfunction

There was an imbalance in reporting of relevant AEs (Table 12).

Table 12. Nephritis / renal dysfunction AEs.

Preferred Term (%)	Nivolumab 3 mg/kg N = 131			Docetaxel N = 129		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	7 (5.3)	3 (2.3)	0	3 (2.3)	0	0
BLOOD CREATININE INCREASED	6 (4.6)	1 (0.8)	0	2 (1.6)	0	0
RENAL FAILURE	1 (0.8)	1 (0.8)	0	0	0	0
TUBULOINTERSTITIAL NEPHRITIS	1 (0.8)	1 (0.8)	0	0	0	0
RENAL FAILURE ACUTE	0	0	0	1 (0.8)	0	0

Median time to onset of renal AEs was 3.9 weeks in the nivolumab arm, although the TIN case occurred at 24.1 weeks. Renal AEs resolved in 4/7 cases, over a median of 12.9 weeks. Three of 7 nivolumab subjects were given systemic corticosteroids (including 1 requiring methylprednisolone).

In Study 063 (Addendum 1), 12% of patients reported relevant renal AEs (mild-moderate in all cases), although only 3.4% of patients had drug related events. In Study 003, renal AEs were similarly prominent.

Endocrine events

There was an imbalance in reporting of endocrine AEs (Table 13).

Table 13. Endocrine AEs.

Sub Category (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 131			Docetaxel N = 129		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	9 (6.9)	0	0	3 (2.3)	0	0
THYROID DISORDER	8 (6.1)	0	0	2 (1.6)	0	0
HYPOTHYROIDISM	7 (5.3)	0	0	0	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	2 (1.5)	0	0	1 (0.8)	0	0
HYPERTHYROIDISM	0	0	0	1 (0.8)	0	0
DIABETES	1 (0.8)	0	0	1 (0.8)	0	0
DIABETES MELLITUS	1 (0.8)	0	0	1 (0.8)	0	0

Median time to onset of any such endocrine AE in the nivolumab arm was 6.6 weeks. Only 3 of 9 endocrine AEs were considered resolved for nivolumab subjects, due to ongoing use of replacement therapy. The CSR stated that events were well controlled with replacement therapies.

No cases of thyroiditis, hypophysitis or adrenal insufficiency were reported in either arm.

Rash

Urticaria and pruritus were more frequent in the nivolumab arm (8.4% in total; one case grade 3) than in the docetaxel arm (2.3%). Otherwise, there was no major imbalance.

Relationship between immune related AEs and efficacy

The sponsor analysed whether occurrence of such immune mediated AEs affected OS, with no sign of an adverse correlation.

Further comments about select AEs in Study 063 (Final CSR)

In Study 063, 47% of subjects were given immune modulating medicines to treat AEs. Usually systemic corticosteroids were used. A summary of select AEs in Study 063 is included. Notable was a case of grade 3 adrenal insufficiency, treated with methylprednisolone and prednisone, resolving after 1.1 weeks. There were no cases of colitis reported (all gastrointestinal select AEs were events of diarrhoea). There were 5 drug related cases of pneumonitis; 3 were severe; all subjects had corticosteroids; all events resolved. Median time to onset for pulmonary select events was 6.1 weeks.

Further comments about select AEs in Study 003 (Final CSR)

Select AEs in the NSCLC cohort (n = 129, including SQ and NSQ NSCLC) had patterns consistent with those observed in 003 and 017.

Post marketing data

No post marketing safety data were supplied.

Evaluator's conclusions on safety

Nivolumab's safety has been characterised in sufficient depth, considering its proposed use as an agent to treat SQ NSCLC. This class of agent is known to produce immune mediated AEs, and studies 017, 063 and 003 revealed a distinct spectrum of 'select AEs' (pneumonitis, etcetera). Beyond these immune mediated AEs, many reported AEs were consistent with symptoms of advanced lung cancer. In the pivotal Study 017, toxicity of nivolumab was distinct from that of docetaxel; the most obvious difference was the significant decrease in haematological toxicity with nivolumab. Several signal were not clearly related to immune related reactions (but might be): the increased frequency of cough (relative to docetaxel), and the occurrence of hypercalcaemia.

First round benefit-risk assessment

First round assessment of benefits

The benefits of nivolumab in the proposed usage (treatment of SQ NSCLC after progression on prior chemotherapy) are:

- Improvement in OS, with a hazard ratio for death of 0.59 relative to a widely used comparator (docetaxel). 42% of nivolumab subjects were alive at 12 months versus 24% of docetaxel subjects. Efficacy appeared to be maintained in subjects receiving nivolumab as a 3rd or subsequent line agent.
- Durability of Anti-tumour responses, relative to docetaxel (for example, 12.5% of nivolumab subjects versus 2.9% of docetaxel subjects had an ongoing objective response in Study 017).
- No apparent decrease in quality of life, while on treatment (although there is uncertainty about impact on quality of life, because many patients did not return questionnaires).
- Marked reduction of myelosuppression and risk of infection; absence of alopecia

First round assessment of risks

The risks of nivolumab in the proposed usage are:

- Onset of immune mediated adverse reactions. Commoner such reactions in the studies of SQ NSCLC were diarrhoea and pruritus. Pneumonitis, nephritis and endocrine system reactions were also prominent. It is likely any bodily system can be affected in this way. Most of these immune mediated reactions appear manageable by early recognition, dose deferral or discontinuation, and/or use of corticosteroids. There was a high rate of steroid use to manage immune related AEs in patients on nivolumab.
- Relatively high frequency of cough, potentially related to subclinical pneumonitis.
- Potential for development of hypercalcaemia, of unclear cause.

First round assessment of benefit-risk balance

The benefit-risk balance of nivolumab (3 mg/kg every 2 weeks), given as monotherapy in treatment of SQ NSCLC after progression on chemotherapy, is favourable at the population level. This is demonstrated by the OS advantage conferred relative to a widely used comparator (docetaxel 75 mg/m^2 every 3 weeks), the apparent absence of any reduction in quality of life relative to docetaxel, and the differing but overall favourable toxicity profile relative to docetaxel.

First round recommendation regarding authorisation

Approval is recommended for this extension of nivolumab's indications. The sponsor has proposed the following indication in SQ NSCLC:

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

In the pivotal and supportive SQ NSCLC trials of nivolumab, use was as monotherapy. This should be reflected in the indication. A preferable wording of the indication is:

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

Clinical questions

Multiple questions and the sponsor's responses relating to clarification and interpretation of the data are listed in the Extract from the Clinical Evaluation Report – consult Attachment 2.

Second round benefit-risk assessment

Unchanged from first round evaluation, that is:

> *The benefit-risk balance of nivolumab (3 mg/kg every 2 weeks), given as monotherapy in treatment of SQ NSCLC after progression on chemotherapy, is favourable at the population level. This is demonstrated by the OS advantage conferred relative to a widely used comparator (docetaxel 75 mg/m^2 every 3 weeks), the apparent absence of any reduction in quality of life relative to docetaxel, and the differing but overall favourable toxicity profile relative to docetaxel.*

Second round recommendation regarding authorisation

Unchanged from first round evaluation.

VII. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU-Risk Management Plan (EU-RMP) for melanoma (Version: 1.1, dated 4 February 2015); EU-RMP for SQ NSCLC (Version: 1.1, dated 4 March 2015); with an Australian Specific Annex (ASA) Version: 1, dated 23 March 2015, which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 14.

Table 14: Ongoing safety concerns for nivolumab.

Important identified risks	Immune mediated adverse reactions Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) Thyroid disorder (hypothyroidism, hyperthyroidism) Uveitis Colitis Type I diabetes mellitus Nephritis Pneumonitis Infusion related reactions
Important potential risks	Immune mediated adverse events Myositis Severe skin reactions
Missing information	Safety in patients with moderate or severe hepatic impairment Safety in patients with severe renal impairment Safety in patients with active systemic autoimmune disease Safety in patients with HIV or Hepatitis B or C Safety in paediatric patients Reproductive and lactation data Long term safety Safety in various ethnic groups Potential pharmacodynamics interaction with systemic immunosuppressants Safety in patients with previous hypersensitivity to another monoclonal antibody Safety in patients ongoing ipilimumab-related adverse events

RMP reviewer comment

Notwithstanding the evaluation of the nonclinical and clinical aspects of the Safety Specification, the sponsor should systematically identify and justify any differences between the above associated summaries of the safety concerns and missing information. Any subsequent changes to the summary of the safety concerns and missing information for nivolumab as specified in the ASA must be entirely captured in a revised ASA to be provided to the TGA for review. In addition, consideration must be given to proposing appropriate pharmacovigilance and risk minimisation activities for any new ongoing safety concerns, to be reflected accordingly in the revised ASA.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified safety concerns and missing information. This includes monitoring ongoing Phase III clinical trials for the important potential risk: 'Immunogenicity' and a PIP as agreed with the EMA for the missing information: 'Paediatric patients'.

Module SIV Section 2.4.3.1: 'Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programs – Children' of the EU-RMPs state:

> *A PIP is agreed by the EMA (P/0064/2014) for the condition of "Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue)" and targets 2 paediatric indications:*
>
> - *"Treatment of a paediatric malignant PD-L1-positive solid tumour in paediatric patients from 6 months to less than 18 years old."*
> - *"Treatment of patients with unresectable or metastatic melanoma in the age group from 12 to less than 18 years old."*
>
> *A waiver for the paediatric population from birth to less than 6 months of age has been granted on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to fulfill a therapeutic need of the specified paediatric subset(s).*

The ASA states:

> *The PV practices in Australia are conducted in accordance with TGA guidance and those outlined in the EU RMP's attached. Specifically, PV activities in Australia are managed at Bristol-Myers Squibb Australia Pty Ltd as part of the Bristol-Myers Squibb Global Pharmacovigilance and Epidemiology group.*

To further characterise all the specified important identified risks a multinational (including Australia) post marketing pharmacoepidemiology study is planned - Study CA209234 titled: 'Pattern of Use, Safety, and Effectiveness of Nivolumab in Routine Oncology Practice'. A draft protocol synopsis for this study (Version: Synopsis 01, dated 5 February 2015) is provided in Annex 6: 'PROTOCOLS FOR PLANNED AND ONGOING STUDIES IN CATEGORIES 1 - 3 OF THE SECTION "SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES" IN PART III' of the EU-RMPs. The anticipated submission of the final clinical study report is 4Q 2024.

RMP reviewer comment

In principle, there are no objections to the proposed pharmacovigilance plan. Nevertheless, the planned studies in a PIP are considered to be additional pharmacovigilance activities. Consequently, the sponsor should amend Table 4-1: 'Safety Concerns and Overview of Planned PV Activities' of the ASA accordingly and provide an assurance that the protocols for these studies will be attached to the ASA once they become available.

Further, the Advisory Committee on the Safety of Medicines (ACSOM) will be asked to comment on the adequacy of the planned post marketing pharmacoepidemiology study to further characterise all the specified important identified risks.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities for all the specified safety concerns and missing information are sufficient, except for all of the specified immune related adverse reactions. Additional risk minimisation activities, in the form of a healthcare professional (HCP) and a patient communication tool, are proposed for these important identified risks.

RMP reviewer comment

In principle, there are no objections to the sponsor's conclusion, which appears reasonable.

Reconciliation of issues outlined in the RMP report

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

The sponsor's correspondence dated 2 July 2015 states that an updated and consolidated EU-RMP for Opdivo (Version: 3.0) with an updated ASA will be submitted during this registration process. However, such documentation was not submitted with the sponsor's response dated 7 August 2015. Therefore, it is unclear how the changes to the revised EU-RMP have been reflected in the ASA and the implications for implementation in Australia. Consequently until adequate RMP documentation is submitted no suggested wording for conditions of registration, as they relate to the RMP, can be provided.

Sponsor response

The sponsor has submitted an updated and consolidated EU-RMP (Version: 3.0, dated 19 June 2015) with an updated ASA (Version: 2, dated 11 August 2015).

Evaluator's comment

This is acceptable. However, no substantive justification has been provided for the omission the important potential risk: 'Cardiac arrhythmias (previously treated melanoma indication only)' for which the EMA has required routine pharmacovigilance and risk minimisation activities. The sponsor should provide compelling justification for the omission of this safety concern or alternatively include it in a revised ASA giving consideration to proposing appropriate pharmacovigilance and risk minimisation activities, before this application is approved.

Recommendation #2 in RMP evaluation report

It is also noted that additional data from Study CA209067: 'A Phase 3, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab Versus Ipilimumab Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma' is yet to be evaluated by the TGA. Safety considerations may be raised by the clinical evaluator through such evaluation. It is important to ensure that response to this evaluation includes a consideration of the relevance for the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue within the RMP.

Sponsor response

The sponsor has not directly responded to this issue.

Evaluator's comment

Given the comments from the clinical evaluation report on the safety specification of the RMP, no response is acceptable.

Recommendation #3 in RMP evaluation report

The sponsor should address the discrepancies raised in the nonclinical evaluation report (see 'Comments on the safety specification of the RMP' below). In addition, the sponsor should adequately address the following issues raised in the clinical evaluation report before this application is approved:

- Given the clinical data suggest that combination therapy may be associated with significantly greater toxicity than nivolumab monotherapy, it is recommended that this observation be emphasised by the healthcare provider and patient communication tools to facilitate safe and effective use of nivolumab in post market use.
- Given severe/life threatening dermatological AEs appear to occur with nivolumab, it is recommended that the important identified risk: 'Immune-related rash' for both monotherapy and combination therapy be renamed as 'Immune-related rash **and severe skin reactions**' in the ASA.
- As stated by the clinical evaluator:

  > *With regard to the list of important risks and missing information, hypercalcaemia should be added to the list of important identified risks.*

  Consideration must also be given to proposing appropriate pharmacovigilance and risk minimisation activities for any new ongoing safety concerns, to be reflected accordingly in a revised ASA.

Sponsor response

1. No direct response to the discrepancies raised in the nonclinical evaluation report could be found.
2. The sponsor states:

   > *As the frequency of most immune-related adverse reactions is increased with the combination of nivolumab and ipilimumab, the sponsor commits to ensuring this point is reinforced in the above educational materials.*

3. The sponsor states:

   > *the EU RMP captures this safety concern appropriately, but noting the TGA's recommendation, agrees to rename this safety concern in the ASA as 'Immune-related rash and severe skin reactions'.*

4. The sponsor has provided justification as to why no further action is required to update the ASA as hypercalcaemia is no longer considered a safety concern by the clinical evaluator.

Evaluator's comment

The sponsor should refer back to the TGA Round 2 RMP Advice (dated 30 September 2015) and adequately address the issue regarding discrepancies raised in the nonclinical evaluation report before this application is approved.

This sponsor's second statement is acceptable.

This sponsor's third statement is acceptable, except that the ASA does not reflect this change. The sponsor should revise the ASA accordingly, before this application is approved.

Correspondence from the Delegate dated 16 November 2015 confirms the sponsor's position in the fourth statement. This is acceptable.

Recommendation #4 in RMP evaluation report

It was reiterated to the sponsor to systematically identify and justify any differences between the summaries of the safety concerns and missing information for the anti PD-1 products, nivolumab and pembrolizumab. Any subsequent changes to the summary of the safety concerns and missing information for nivolumab must be entirely captured in a revised ASA giving consideration to proposing appropriate pharmacovigilance and risk minimisation activities, before this application is approved. The ACSOM also stated:

> *The committee advised that as nivolumab is the second drug in the class of PD-1 checkpoint inhibitors, all safety concerns identified for pembrolizumab (first drug in the class of PD-1 checkpoint inhibitors) should also be included in the summary of safety concerns for nivolumab, or their omission justified.*

Sponsor response

The sponsor has again declined to provide any description of the differences between the profiles of the two agents on the basis of the limitations of interpreting any such comparison and the lack of access to the proprietary safety database for pembrolizumab.

Evaluator's comment

Information about the safety profile of pembrolizumab is available in the publically available Australian PI for pembrolizumab. Furthermore, as expected the summaries of the safety concerns and missing information for the anti PD-1 products, nivolumab and pembrolizumab, are quite similar with the main differences being in the missing information category. Consequently, this issue remains outstanding and should be adequately addressed before this application is approved.

Recommendation #5 in RMP evaluation report

It was reiterated to the sponsor that the planned studies in the PIP were considered by the TGA to be additional pharmacovigilance activities proposed to further characterise the missing information: 'Paediatric patients < 18 years of age'. Consequently the sponsor was asked to amend only Table 4-1: 'Safety Concerns and Overview of Planned PV Activities' of the ASA (not the EU-RMP) accordingly and provide an assurance that the protocols for these studies will be attached to the ASA once they become available.

Sponsor response

The sponsor again maintains its position that the planned paediatric studies are not part of the Pharmacovigilance Plan until a paediatric indication is sought, as this is the EMA's approach to apparently avoid the need to update the RMP every time the PIP is updated.

Evaluator's comment

Consistent with the current RMP guidelines dated 4 May 2015 on the TGA website, an updated RMP should be submitted whenever there is a **significant material change** to the RMP. Further, the logic of the sponsor's rationale is considered to be flawed. Consequently, this issue remains outstanding and should be adequately addressed before this application is approved.

Recommendation #6 in RMP evaluation report

The following recommendations were made to the Delegate regarding the proposed indications and the draft Consumer Medicines Information (CMI) document and remain outstanding:

- When the US FDA approved the melanoma indication, this approval stated:

  > *This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.*

  If applicable, it is recommended to the Delegate that similar statements alluding to an absence of efficacy data be included in the 'Indications' section of the Australian PI. Any such change should be adequately reflected in the draft Consumer Medicine Information (CMI) document.

- In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the first sentence under the heading: 'What is Opdivo used for' in the draft CMI document be revised to:

  > *Opdivo contains the active substance nivolumab, a protein* ***produced in Chinese hamster ovary cells****, which helps your immune system to attack and destroy cancer cells.*

  This is consistent with the draft PI and will alert patients who have a known allergy to proteins derived from this source.

Sponsor response

The sponsor has not directly responded to this issue.

Evaluator's comment

These recommendations to the Delegate regarding the proposed indications and the draft CMI document remain outstanding.

Recommendation #7 in RMP evaluation report

The sponsor was asked to address each issue raised in the ACSOM advice and that any subsequent changes to the pharmacovigilance and/or risk minimisation activities in Australia for Opdivo must be entirely captured in a revised ASA to be provided to the TGA for review before this application is approved.

Sponsor response

The sponsor responds to a number of issues raised in the ACSOM advice and states inter alia:

> *the sponsor does not agree to have an additional surveillance requirement for Australian patients.*

Also refer to Recommendation 4.

Evaluator's comment

The sponsor's response to committee's concerns about the proposed design and conduct of the planned post marketing pharmacoepidemiology study (CA209234) are not entirely satisfactory. However, the sponsor's correspondence to the Delegate dated 14 October 2015 indicates that a planned observational safety Study CA209401 is to be conducted in Australian centres. This would appear to directly address the committee's concerns mentioned above. However, no reference to or detail about this study as an additional pharmacovigilance activity for specified ongoing safety concerns has been included in the ASA. In fact, Section 4 of the ASA states:

No additional PV activities specific to Australia are planned

and Table 4-1 of the ASA has been deleted. The sponsor should revise the ASA accordingly, including the reinstatement of Table 4-1: 'Safety Concerns and Overview of Planned PV Activities' and the provision of the protocol for this study as an attachment to the ASA, before this application is approved.

Summary of recommendations

It is considered that the sponsor's response to the TGA Section 31 request has not adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

The ASA states:

> *This ASA accompanies the nivolumab EU RMP v3. This document includes a description of BMS's risk management plan based on all information BMS deems relevant to the safety profile of nivolumab. BMS wishes to note that cardiac arrhythmia is included in the EU RMP v3 as an important potential risk (for pre-treated melanoma only) on the basis of a requirement by the European Medicines Agency (EMA). BMS wishes to clarify that it does not consider this addition to represent an activity that is necessary to ensure patient safety and proper use of the product based on available evidence.*

No substantive justification has been provided for the omission of this safety concern for which the EMA has required routine pharmacovigilance and risk minimisation activities. The sponsor should provide compelling justification for the omission of this safety concern or alternatively include the important potential risk: 'Cardiac arrhythmias (previously treated melanoma indication only)' in a revised ASA giving consideration to proposing appropriate pharmacovigilance and risk minimisation activities, before this application is approved.

The sponsor was asked to address the discrepancies raised in the TGA nonclinical evaluation report for Opdivo, but no direct response to this issue could be found. The sponsor should refer back to the TGA Round 2 RMP Advice (dated 30 September 2015) and adequately address this outstanding issue before this application is approved.

The sponsor was asked to respond to safety considerations raised by the clinical evaluators through the consolidated Section 31 request and/or the clinical evaluation reports, in the context of relevance to the RMP. In this context, it was observed that severe/life-threatening dermatological adverse events appear to occur with the use of nivolumab. Therefore, it was recommended that the important identified risk: 'Immune-related rash' for both monotherapy and combination therapy be renamed as 'Immune-related rash **and severe skin reactions**' in the ASA. The sponsor states it:

> *believes that the EU RMP captures this safety concern appropriately, but noting the TGA's recommendation, agrees to rename this safety concern in the ASA as* ***'Immune-related rash and severe skin reactions'.***

This is acceptable, except that the ASA does not reflect this change. The sponsor should revise the ASA accordingly, before this application is approved.

It was reiterated to the sponsor to systematically identify and justify any differences between the summaries of the safety concerns and missing information for the anti-PD-1 products, nivolumab and pembrolizumab. Any subsequent changes to the summary of the safety concerns and missing information for nivolumab must be entirely captured in a

revised ASA giving consideration to proposing appropriate pharmacovigilance and risk minimisation activities, before this application is approved. The ACSOM also stated:

> *The committee advised that as nivolumab is the second drug in the class of PD-1 checkpoint inhibitors, all safety concerns identified for pembrolizumab (first drug in the class of PD-1 checkpoint inhibitors) should also be included in the summary of safety concerns for nivolumab, or their omission justified.*

Nevertheless, the sponsor has again declined to provide any description of the differences between the profiles of the two agents on the basis of the limitations of interpreting any such comparison and the lack of access to the proprietary safety database for pembrolizumab. However, information about the safety profile of pembrolizumab is available in the publically available Australian PI for pembrolizumab. Further, as expected the summaries of the safety concerns and missing information for the anti PD-1 products, nivolumab and pembrolizumab, are quite similar with the main differences being in the missing information category. Consequently, this issue remains outstanding and should be adequately addressed before this application is approved.

It was reiterated to the sponsor that the planned studies in the PIP were considered by the TGA to be additional pharmacovigilance activities proposed to further characterise the missing information: 'Paediatric patients < 18 years of age'. Consequently, the sponsor was asked to amend only Table 4-1: 'Safety Concerns and Overview of Planned PV Activities' of the ASA (not the EU-RMP) accordingly and provide an assurance that the protocols for these studies will be attached to the ASA once they become available. Nevertheless, the sponsor again maintains its position that the planned paediatric studies are not part of the Pharmacovigilance Plan until a paediatric indication is sought, as this is the EMA's approach to apparently avoid the need to update the RMP every time the PIP is updated. Consistent with the current RMP Guidelines dated 4 May 2015 on the TGA website, an updated RMP should be submitted whenever there is a **significant material change** to the RMP. Further, the logic of the sponsor's rationale is considered to be flawed. Consequently, this issue remains outstanding and should be adequately addressed before this application is approved.

The following recommendations were made to the Delegate regarding the proposed indications and the draft CMI document and remain outstanding:

- When the US FDA approved the melanoma indication this approval stated:

  > *This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.*

- If applicable, it is recommended to the Delegate that similar statements alluding to an absence of efficacy data be included in the 'Indications' section of the Australian PI. Any such change should be adequately reflected in the draft consumer medicine information document.

- In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the first sentence under the heading: 'What is Opdivo used for' in the draft consumer medicine information document be revised to:

  > *Opdivo contains the active substance nivolumab, a protein produced in Chinese hamster ovary cells, which helps your immune system to attack and destroy cancer cells.*

  This is consistent with the draft PI and will alert patients who have a known allergy to proteins derived from this source.

Section 1.2.1: 'ARTG Registration Status for Opdivo (Nivolumab)' of the ASA should be corrected to reflect that Opdivo, as monotherapy is proposed to be indicated for the

treatment of locally advanced or metastatic NSQ NSCLC with progression on or after prior chemotherapy via the submission of the concurrent application (for NSQ NSCLC).

Advice from the ACSOM

The sponsor was asked to address each issue raised in the ACSOM advice and that any subsequent changes to the pharmacovigilance and/or risk minimisation activities in Australia for Opdivo must be entirely captured in a revised ASA to be provided to the TGA for review before this application is approved. In addition to the ACSOM comment previously mentioned, the sponsor's response to committee's concerns about the proposed design and conduct of the planned post marketing pharmacoepidemiology study (CA209234) are not entirely satisfactory. However, the sponsor's correspondence to the Delegate dated 14 October 2015 states:

> *BMS can confirm for the TGA that the inclusion criteria for Study CA209234 includes treatment of patients with commercial nivolumab for the first time, alone or in combination with ipilimumab, for approved indications in melanoma.*
>
> *In addition to this study, BMS is also planning a separate and distinct observational safety study to measure adverse event outcomes of combination therapy with nivolumab and ipilimumab in the treatment of unresectable or metastatic melanoma in Australian centres. Study CA209401 (Clinical Trial of Nivolumab Combined with Ipilimumab Followed by Nivolumab Monotherapy as First-Line Therapy of Subjects with Histologically Confirmed Stage III (Unresectable) or Stage IV Melanoma. **CheckMate** 401: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 401) is being conducted internationally and includes 20 Australian centres with a plan to recruit 5 patients per centre. A copy of the protocol for Study CA209401 is provided (please see Attachment 3).*
>
> *Both observational studies, CA209234 and CA209401, aim to provide data on safety outcomes from the use of combination therapy in the treatment of patients with unresectable or metastatic melanoma in routine clinical practice and provide the opportunity for further clinical experience in managing patients with the combination.*

It would appear the planned observational safety Study CA209401 to be conducted in Australian centres directly address the committee's concerns mentioned above. However, no reference to or detail about this study as an additional pharmacovigilance activity for specified ongoing safety concerns has been included in the ASA. In fact, Section 4: 'Pharmacovigilance Plan' of the ASA states: "No additional PV activities specific to Australia are planned" and Table 4-1: 'Safety Concerns and Overview of Planned PV Activities' of the ASA has been deleted. The sponsor should revise the ASA accordingly, including the reinstatement of Table 4-1: 'Safety Concerns and Overview of Planned PV Activities' and the provision of the protocol for this study as an attachment to the ASA, before this application is approved.

Comments on the safety specification of the RMP

Clinical evaluation report

Not applicable.

Key changes to the updated RMP

In their response to the TGA Round 2 RMP Advice the sponsor provided an updated EU-RMP (Version: 3.0, dated 19 June 2015) with an updated ASA (Version: 2, dated 11 August 2015). Key changes from the versions evaluated at Round 1 are summarised below in Table 15.

Table 15. Key changes to the updated RMP.

	Key changes to the updated RMP
EU-RMP	Inclusion of NSQ NSCLC indication Inclusion of nivolumab in combination therapy with ipilimumab in advanced melanoma indication Immune-related rash was added as an Important Identified Risk (including monotherapy) Encephalitis was added as an Important Identified Risk under Other Immune-Related Adverse Reactions Cardiac Arrhythmia was added as an Important Potential Risk (for pre-treated melanoma only)
ASA	Revised in relation to the new information in the updated EU-RMP Deletion of Table 3-1: 'Summary of Safety Concerns for Nivolumab Monotherapy Compared with Nivolumab and Ipilimumab Combination Therapy' Deletion of Table 4-1: 'Safety Concerns and Overview of Planned PV Activities' Addition of Section 5.2: 'Evaluation of Additional Risk Minimisation Activities in Australia' Provision of the draft HCP and patient communication tools (as attachments to the ASA)

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

At this time no wording can be provided, as it is recommended that an acceptably revised ASA be submitted before this application is approved.

VIII. Overall conclusion and risk/benefit assessment

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

Quality

The ACPM Summary Quality was considered.

A GMP clearance was due to expire 23 October 2015; this issue is being followed up. Otherwise, there were no objections. Batch release conditions of registration were recommended.

Nonclinical

The nonclinical evaluation report and a follow-up note for file were considered.

Pregnancy Category D was recommended:

> *A pre/postnatal study in monkeys showed increased in pregnancy and infant loss, consistent with the effect of PD-1 blockade.*

The sponsor has accepted this recommendation.

Clinical

There were three separate clinical evaluation reports, as follows:

- for melanoma:
  - the main CER ("MEL"); and
  - a supplementary report ("suppl. CER") for Study 067 (this also updated the clinical evaluator's recommendations in melanoma)
- for squamous cell NSCLC:
  - one report ("SQ NSCLC CER")

Melanoma data evaluation

Overview of data

For nivolumab monotherapy, pivotal studies were:

- Study 066 (Phase III; versus dacarbazine; first line in BRAF WT [wild type] patients);
- Study 037 (Phase III; versus choice of chemo; second or third line), and
- Study 067 (Phase III; versus IPI [ipilimumab], as well as versus 'nivolumab + IPI'; first-line).

For nivolumab in combination with ipilimumab, pivotal studies were:

- Study 067 (as above)
- Study 069 (Phase II; versus IPI; first line); and

Further studies, for example, Phase I studies, are mentioned in the MEL clinical evaluation report.

Clinical evaluator's view

The clinical evaluator's views are integrated in the supplementary clinical evaluation report:

> *The benefit-risk balance of nivolumab monotherapy, given the proposed usage, is favourable. The drug has better efficacy and comparable or better safety than conventional chemotherapy or ipilimumab.*
>
> *Given that nivolumab monotherapy has better efficacy and safety than ipilimumab, it should be preferred over ipilimumab for the treatment of advanced melanoma. Regulatory approval for combination therapy should only be considered if the combination has a more favourable benefit-risk balance than nivolumab alone. A statistically significant improvement in efficacy for combination treatment over nivolumab monotherapy has not been established, as Study CA209067 was not designed to demonstrate this. However the study clearly demonstrates that the combination is associated with a significant increase in toxicity. It is therefore not*

possible to conclude that combination treatment is associated with a more favourable benefit-risk balance than nivolumab monotherapy.

The evaluator's recommendation is as follows:

It is recommended that the application for monotherapy should be approved. The proposed monotherapy indication is acceptable. It is recommended that the application for use in combination with ipilimumab be rejected due to uncertain evidence of efficacy, and concerns regarding increased toxicity, when compared to nivolumab monotherapy.

Pharmacology

The evaluator notes that two studies (MDX-1106-01 and MDX-1106-03, that is, Study 003) included intensive PK sampling. In other studies, there was only sparse sampling, contributing to Population PK analyses.

The clinical evaluator considered that the PK data in the submission were acceptable, but did also note the absence/insufficiency of clinical data concerning:

- Plasma protein binding
- Tissue distribution
- Use in moderate to severe hepatic impairment
- Use in severe renal impairment

Outcomes of PD studies did not raise clinical issues.

The sponsor conducted a series of population PK analyses. These are detailed in the SQ NSCLC clinical evaluation report. There was also a Population PK evaluation, which informed a discussion by the Pharmaceutical Subcommittee (PSC).

Efficacy

A 3 mg/kg Q2W dose has been selected for monotherapy use in melanoma.

Study 066

Study 066 (Phase III; versus dacarbazine; first line in BRAF WT patients) is discussed in the clinical evaluation report. The primary endpoint was OS. A total of 206 patients were treated with nivolumab, 205 with dacarbazine. The study was amended as evidence emerged of better survival in the nivolumab arm, allowing crossover to nivolumab (efficacy data use a database lock of 5 August 2014, prior to crossover). 61% of patients had stage IV M1c disease[41] at baseline; 35% had PD-L1+ tumours; 37% had LDH > ULN. The HR for OS was 0.42 (95% CI 0.30 to 0.60) favouring nivolumab; median OS was 10.8 months for dacarbazine, and not reached for nivolumab. All subgroups of OS showed benefit versus dacarbazine. 12/54 nivolumab patients (22%) had a >30% reduction (versus baseline) in target lesion size with treatment beyond progression.

Study 037

Studied patients had progressed on IPI (and a BRAF inhibitor where appropriate). ORR was the only primary endpoint analysed in the interim report under evaluation; a 31.7% ORR was seen for nivolumab, versus 10.6% for chemotherapy. However, an early OS analysis requested by the FDA showed no survival benefit (HR 0.96). In an updated OS analysis, again **no** OS benefit was observed. The sponsor pointed to: immaturity of survival data (final OS analysis due ~Feb 2016); imbalance in brain metastases and elevated LDH favouring survival in the chemo arm; good OS in the chemo arm versus historical

[41] Stage M1c: metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH level.

outcomes for such chemo; and confounding of outcomes due to subsequent use of pembrolizumab in the chemo arm.

Study 067

Study 067 (Phase 3; versus IPI, as well as versus 'nivolumab + IPI'; first line) is evaluated in a supplementary clinical evaluation report. Randomisation was to:

- Arm A: Nivolumab 3mg/kg IV every 2 weeks;
- Arm B: Ipilimumab 3 mg/kg IV and nivolumab 1 mg/kg IV every 3 weeks for 4 treatments; then nivolumab 3 mg/kg IV every 2 weeks;
- Arm C: Ipilimumab 3 mg/kg every 3 weeks for 4 treatments.

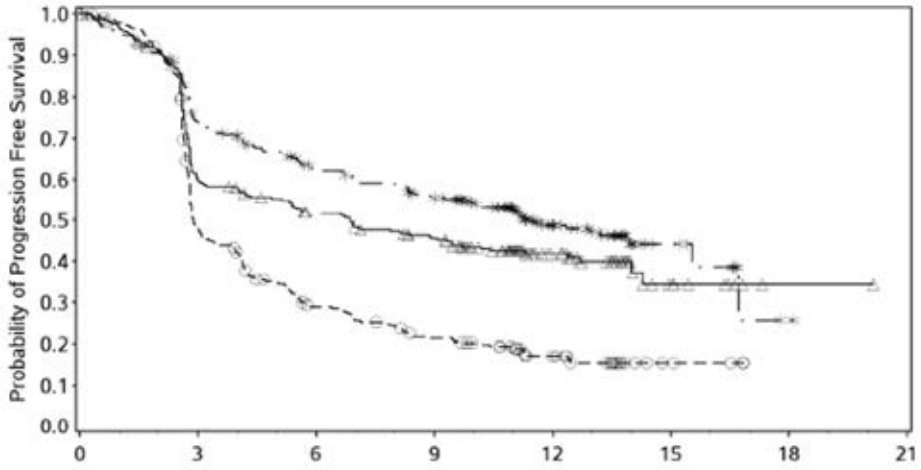
The co-primary endpoints were PFS and OS. The study formally examined nivolumab monotherapy versus IPI monotherapy, and combination therapy versus IPI monotherapy. The sponsor considered comparison of nivolumab monotherapy versus combination therapy to be descriptive.

There were slight age and ECOG Performance Status imbalances favouring the nivolumab monotherapy arm, and a history of brain metastases was recorded in 2.5% (nivolumab) versus 3.5% (combination) versus 4.8% (IPI); otherwise, baseline characteristics were broadly balanced. A total of 116 Australians were included in the study, via 15 investigators, out of 945 randomised subjects.

Progression free survival (PFS)

The CSR only presented final PFS results, as follows: 55.1% of nivolumab patients had progressed or died; 48.1% of combination patients had progressed or died; and 74.3% of IPI patients had progressed or died. Kaplan-Meier curves follow for PFS (Figure 3).

Figure 3. Kaplan-Meier plot of PFS per investigator (all randomised subjects).



Number of Subjects at Risk

Nivolumab							
316	177	147	124	50	9	1	0
Nivolumab + Ipilimumab							
314	219	173	151	65	11	1	0
Ipilimumab							
315	137	77	54	24	4	0	0

Nivolumab (events: 174/316), median and 95% CI: 6.87 (4.34, 9.46)
Nivolumab + Ipilimumab (events: 151/314), median and 95% CI: 11.50 (8.90, 16.72)
Ipilimumab (events: 234/315), median and 95% CI: 2.89 (2.79, 3.42)

Nivolumab vs Ipilimumab - hazard ratio and 99.5% CI: 0.57 (0.43, 0.76); p-value: <0.0001
Nivolumab + Ipilimumab vs Ipilimumab - hazard ratio and 99.5% CI: 0.42 (0.31, 0.57); p-value: <0.0001
Nivolumab + Ipilimumab vs Nivolumab - hazard ratio and 95% CI: 0.74 (0.60, 0.92)

Further PFS outcome data are discussed. Of note, the BRAF WT subgroup did better with nivolumab than with IPI (HR 0.77).

PD-L1 tumour status

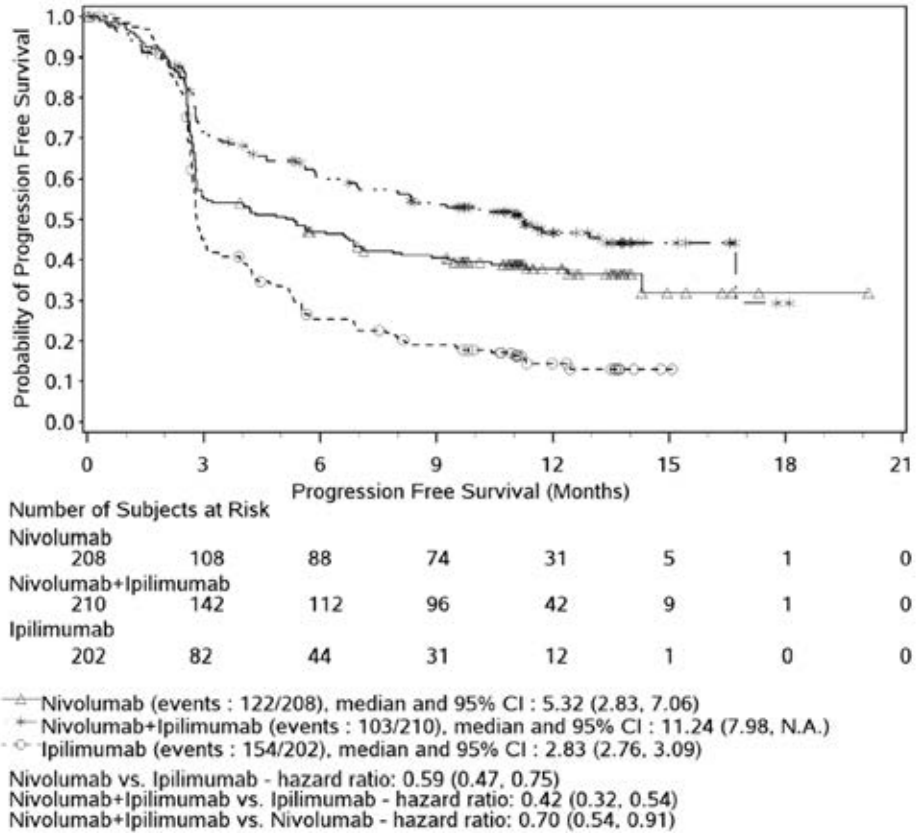
Subgrouping by PD-L1 tumour status is discussed. The evaluator's conclusion is repeated below (bold is added):

> *These analyses indicate that both nivolumab monotherapy and combination therapy are superior to ipilimumab monotherapy, regardless of PD-L1 status. They also suggest that nivolumab monotherapy and combination therapy have similar efficacy in subjects with PD-L1 positive tumours, but that* ***combination therapy may be more effective than nivolumab monotherapy in subjects with PD-L1 negative tumours****.*

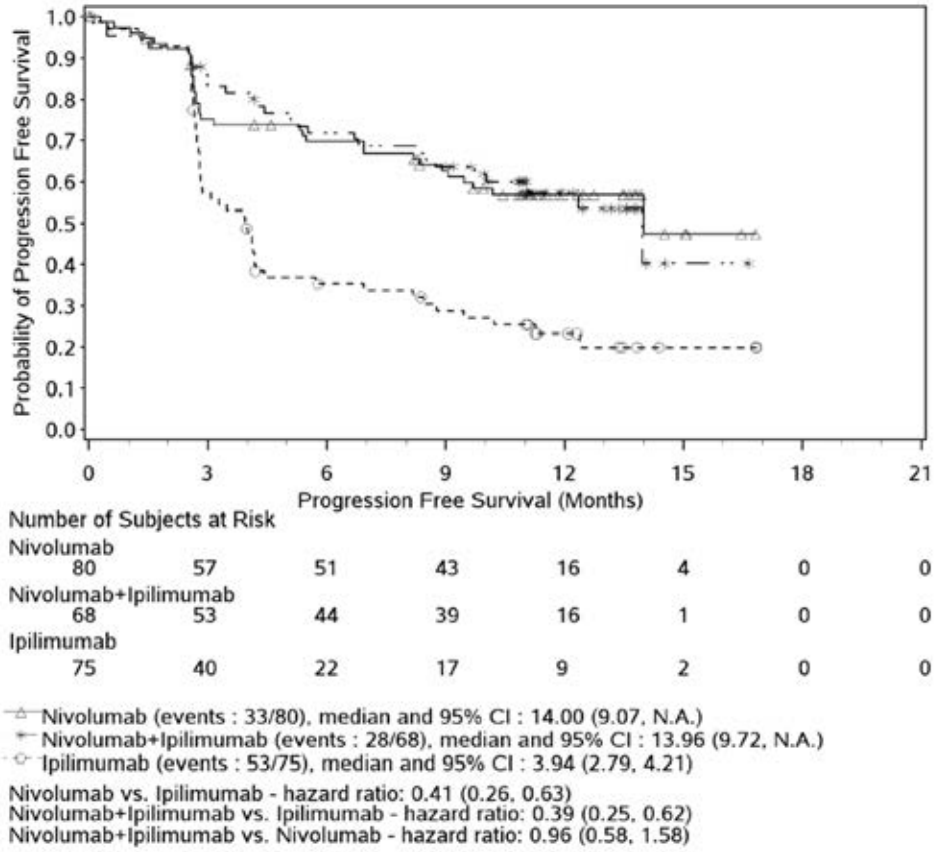
Kaplan-Meier curves of PFS using a PD-L1 threshold of 5%, taken from the sponsor's combination therapy Clinical Overview, illustrate this conclusion (Figure 4).

Figure 4. PD-L1 expression cutoff: 5%.

(a) PD-L1 negative subjects



(b) PD-L1 positive subjects



An exploratory PFS analysis of the subgroup of patients whose tumours had ≥20% PD-L1 expression (33-45 per arm) showed impressive HR versus ipilimumab of 0.31 (nivolumab) and 0.28 (combination therapy).

The sponsor's view is summarised in its Clinical Overview for the combination:

> *The validated PD-L1 IHC analyses demonstrate that PD-L1 expression may be used to understand the risk-benefit of nivolumab + ipilimumab combination therapy in an individual patient but should not be the sole factor used to inform treatment decisions. Although the greatest benefit for the combination of nivolumab + ipilimumab versus nivolumab alone may occur in the setting of low to no PD-L1 expression, clinically meaningful improvement was observed across PD-L1 expression levels.*

Other efficacy endpoints

57.6% of combination arm subjects had an objective response (including 11.5% with a complete response). ORRs for nivolumab and ipilimumab monotherapies were 43.7% and 19.0% respectively.

There was an attempt to assess the impact of treatment of quality of life (QoL); no improvements in QoL were evident.

Study 069

Study 069 (Phase II; versus IPI; first line) is evaluated in the main MEL clinical evaluation report. Dosing was as per the relevant arms of Study 067. A total of 94 subjects were treated with combination therapy and 46 with IPI. Patients with BRAF WT and mutant tumour were enrolled, but the primary efficacy endpoint was ORR in BRAF WT patients. The ORR in BRAF WT patients was 59.7% (combination) versus 10.8% (IPI), and complete responses were seen in 16.7% versus 0% respectively. In the BRAF mutant population,

ORR was 43.5% versus 0%, and complete response rate (CRR) was 17.4% versus 0%, respectively. PFS benefit was evident relative to IPI, regardless of BRAF status. OS data were immature and will be confounded by a high degree of crossover. An updated efficacy report revealed no important new outcomes, except that median duration of response had still not been reached.

Safety

Studies contributing safety data are noted; also, Study 067 contributes relevant data. Patient exposure is tabulated. Safety of nivolumab monotherapy is distinct from that of nivolumab and ipilimumab combination therapy.

Monotherapy

While the type of AEs seen with nivolumab monotherapy differed from the type seen with DTIC and other chemotherapies (Studies 066, 037), the overall frequency of AEs was not different. Nivolumab was associated with half as much nausea/vomiting than dacarbazine, almost no neutropenia/thrombocytopenia, almost no alopecia, but more pruritus, rash, vitiligo, erythema and hypothyroidism.

In Study 066, the frequency of SAEs was slightly lower than with dacarbazine. In Study 037, the frequency of SAEs was distinctly higher than with chemo (44% versus 21.6%), although time on treatment was imbalanced across arms and, as is pointed out, incidence of drug related SAEs in Study 037 was lower for nivolumab than chemotherapy. AEs leading to discontinuation were seen less often with nivolumab than with chemotherapy.

The sponsor defined 'select AEs' (CER page 33): endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis and rash, as well as hypersensitivity (based on previous experience and the mechanism of checkpoint inhibitors). Prominent were skin AEs (48% of nivolumab patients in Study 066) and gastrointestinal AEs (26% of nivolumab patients in Study 066); and thyroid disorders were much more frequent than with chemotherapy. There was also infrequent but consistent reporting of severe or life threatening 'select' events with nivolumab. Select AEs capture only the commoner autoimmune AEs induced by nivolumab; some other such AEs fall outside of this categorisation, for example, demyelinating brain disease, uveitis.

Study 067 allows comparison of the safety of nivolumab and ipilimumab monotherapies. As a general rule, nivolumab had a better safety profile than ipilimumab in this study, for example:

- Drug related serious AEs were reported for 5.8% of nivolumab patients, 16.4% of ipilimumab patients;
- frequency of colitis was 1.6% for nivolumab, but 11.6% for ipilimumab (for other AEs, the difference was less stark).

This general rule was not followed in some categories:

- For skin AEs, the frequency was similar across monotherapy arms, but the frequency of severe or life threatening skin AEs was lower for nivolumab (2.2% versus 4.2%).
- Respiratory AEs were seen to a similar extent across monotherapy arms.
- For LFT derangements frequency was similar, or slightly higher with nivolumab than with IPI; in 1.7% of nivolumab subjects but no IPI subjects, there was concurrent aspartate aminotransferase (AST) or alanine transaminase (ALT) elevation >3xULN and bilirubin (BR) elevation >2xULN within 30 days of treatment.
- For thyroid derangements, the frequency was distinctly higher with nivolumab than with IPI monotherapy, for example, hyperthyroidism, 5.8% versus 1.0% (but no AEs were severe). This did not extend to other endocrinopathies.

- Leukopenia, neutropenia and lymphopenia were more frequent with nivolumab than with IPI, though usually these lab AEs were mild or moderate in grade. The evaluator noted one report of neutropenia associated with sepsis and death, in the nivolumab arm.

Combination therapy

Study 067 allowed formal and informal comparison of the combination approach with both nivolumab and ipilimumab monotherapy.

More AEs were reported in the combination arm than in than either monotherapy arm. In the combination arm there was:

- an increase in the frequency of diarrhoea (31% nivolumab versus 52% combination versus 46% ipilimumab), including an increase in severe or life threatening diarrhoea (3.8% versus 10.5% versus 7.7%)
- a high frequency of colitis (no higher than with IPI): 1.6% versus 12.1% versus 11.6%
- *Question for sponsor: Given diarrhoea is a prominent symptom of colitis, should colitis be considered a 'subset' of the reporting of diarrhoea events? Or, if a patient is classified as having colitis, do events of 'diarrhoea' not get included in the above figures for diarrhoea?*
- a major increase in pyrexia (13% versus 37% versus 17%) (likewise for chills)
- a similar extent of skin AEs (for example, rash 28% versus 32% versus 24%)
- a major increase in pneumonitis (1.9% versus 6.4% versus 2.6%), and more dyspnoea (12% versus 20% versus 13%) but similar reporting of cough (20-22%)
- a dramatic increase in LFT derangements (for example, ALT elevation: 7% versus 20% versus 5%)
- a major increase in endocrinopathies (17% versus 32% versus 12%), for example, hypothyroidism (9% versus 17% versus 5%), hyperthyroidism (6% versus 10% versus 1%) and hypophysitis (0.6% versus 7.7% versus 3.9%)
- an increase in laboratory reporting of elevated lipase (8.0% versus 12.8% versus 6.4%), though lab reporting of amylase elevations was similar (5-7%)
- a moderate increase in laboratory reporting of elevated blood creatinine (1.6% versus 5.8% versus 2.9%)

There was a big increase in the incidence of drug related, severe or life threatening AEs with the combination approach (16% nivolumab versus 55% combination versus 27% IPI), attributable to all AE categories but particularly abnormal laboratory investigations (5% versus 24% versus 7%), within which elevated LFTs and elevated lipase were prominent. Actual drug related hepatobiliary AEs also accounted for much of the difference (1.3% versus 8% versus 0.3%).

The sponsor analysed its nivolumab database for the incidence of 'Hy's Law' cases. Of 2354 patients receiving nivolumab (including 507 receiving nivolumab + ipilimumab), 4 had LFT derangements fulfilling 'Hy's Law', with no alternative cause in 1 patient (who had been given the nivolumab + ipilimumab combination). Another 12 patients fulfilled a broader laboratory definition (again with no alternative cause): 3/1794 on nivolumab monotherapy (0.2%); 7/507 on nivolumab + IPI (1.4%); 2/53 on nivolumab + sunitinib (3.8%). All 12 cases resolved with corticosteroids (and mycophenolate mofetil [MMF] in 1 case).

- *Question for sponsor: Have patients in the 'Hy's law' category or with other significant LFT abnormalities been evaluated for the presence of autoimmune antibodies that may been seen in autoimmune hepatitis?*

There was also an increase in the frequency of severe or life threatening 'serious AEs' (nivolumab, 28% versus combination, 51% versus ipilimumab, 38%).

There was a major increase in the frequency with which AEs led to discontinuation in the combination arm (43%) relative to the nivolumab arm (14%) and the ipilimumab arm (22.5%). Diarrhoea, colitis and elevated LFTs were notable causes, in the combination arm. A similar rate of discontinuation was seen in the Phase II study (069); this was highlighted by the clinical evaluator as a concern. The sponsor notes:

> *In subjects who did discontinue combination therapy due to an adverse event in Study CA209067, 68% (81/120) experienced a complete or partial response. The median time to response was 2.8 months (1.1–10.3), the median duration of response was 13.1 months (NA) and ongoing responses among responders was 56/81 (69).*[42] *Similar patterns of responses in patients who discontinued combination therapy were also observed in Study CA209069 with 68% (38/44) of patients who discontinued combination therapy experiencing a complete or partial response.*

- *Question for sponsor: Is there any information about PFS and OS outcomes in subjects who had to discontinue due to an AE? Is there information about use of subsequent therapies? What proportion of patients moved on to a new line of therapy?*

Death was less frequent in the nivolumab and combination arms than the ipilimumab arm (27.2% nivolumab versus 27.5% combo versus 36.7% IPI), due to less melanoma mortality in the nivolumab containing arms. Deaths due to study drug were rare in Study 067 (n = 1 for nivolumab monotherapy, n = 1 for ipilimumab monotherapy; none in the combination arm), however an 'other' primary reason for death within 100 days of last dose was described for 4.2% in the combination arm, versus <2% in monotherapy arms. Given the increase in toxicity with combination therapy, it is at least plausible that combination therapy toxicity might contribute to many of the primary causes of death mentioned (pulmonary embolism, infection, etcetera).

There was a major rise in anti nivolumab antibodies in the combination arm, relative to nivolumab monotherapy, extending to persistent and neutralising antibodies.

Study 069 also contributed useful safety data for combination therapy. There were some differences in the pattern of AEs, relative to Study 067. For example, in Study 069:

- colitis was more frequent with combination therapy (22%) than with ipilimumab monotherapy (11%)
- hypophysitis was reported even more frequently than in Study 067 (12.8% for the combination arm versus 6.5% for ipilimumab monotherapy)
- pneumonitis or interstitial lung disease was reported even more frequently (9.6% for the combination arm versus 2.2% for ipilimumab monotherapy); one pneumonitis death was described as due to study drug
- again, there was an imbalance in deaths due to 'other' reasons (n = 7 for the combination arm, n = 1 for ipilimumab)

Overall, safety data in Study 069 corroborate the safety signals from Study 067, though for specific AEs such as colitis and hypophysitis, results from the Phase II study suggest that

[42] Larkin J, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *NEJM* 371: 1867-1876 (2014).

Study 067 does not necessarily define the upper limit of toxicity that might be seen with combination therapy.

The sponsor's response to MEL Supplementary clinical evaluation report questions, dated 14 October 2015 integrates the sponsor's views about resolution rates of immune mediated AEs. t is notable that nivolumab monotherapy immune mediated AEs created much less need for infliximab (0.6%, versus 5-6% for other arms).

Squamous non-small cell lung cancer (SQ NSCLC) data evaluation

Overview of data

The pivotal study was Study 017 (Phase III; versus docetaxel; second line).

The main supportive study was Study 063 (Phase II; single arm; third+ line).

The clinical evaluation was by the Delegate, so the evaluator's view is not mentioned here.

Population PK

The PK of nivolumab in SQ NSCLC was characterised by way of population PK analysis.

The final population PK model included effects of baseline weight, eGFR and ECOG status on clearance, and effects of baseline weight, sex and cell type/histology (using the combined SQ and non-squamous groups) on volume of distribution of the central compartment.

The variables were not all considered clinically relevant, that is, magnitude of effect was not necessarily large for each variable. Tumour type was not a clinically relevant predictor of nivolumab PK. Evidently, dosing is weight based, which must address the influence of weight, at least in part.[43] It was also noted that few people with ECOG PS >1 were included in the population PK analysis.

An issue requiring further exploration is the influence of serum albumin on nivolumab PK, either directly or, more likely, by serving as an indicator of significant renal, hepatic or other organ system dysfunction. It seems patients with low baseline serum albumin do have lower $C_{avg,ss}$; this might influence efficacy.

Efficacy

Study 017

Study 017 (Phase III; versus docetaxel; second line) is discussed; the primary endpoint was OS. Patients had advanced SQ NSCLC that had progressed during or after a platinum doublet based chemotherapy regimen. A total of 131 patients were treated with nivolumab, n = 129 with docetaxel. The hazard ratio for OS, in favour of nivolumab, was 0.59 (95% CI 0.43-0.81). Median OS was 9.2 months (nivolumab) versus 6.0 months (docetaxel). There was no major difference in benefit of nivolumab based on tumour PD-L1 status. Other endpoints were supportive of the superior efficacy of nivolumab. The docetaxel arm did not do well relative to historical outcomes with this agent, although many such historical trials were across all NSCLC patients, not just those with squamous histology. The sponsor argued that at least 9 of 28 nivolumab subjects who were treated beyond progression derived some benefit.

Study 063 and Study 003

Study 063 (Phase II; single arm; third or later line) is discussed; the primary endpoint was ORR. A total of 117 subjects were treated; 14.5% had a partial response (there were no

[43] See also BMS 'Clarification of comments raised by the PSC in relation to the POP PK evaluation report' dated 28 July 2015, Comment 1.

complete responses). Median OS was 8.2 months, with no sign of any plateau in the OS curve. There was no clear association between tumour PD-L1 status and efficacy.

Also of note, in Phase I Study 003, there was a marked decrease in objective response in patients receiving 1 mg/kg, at least in NSCLC.

Safety

A total of 248 patients received nivolumab in Study 017 and in Study 063.

Overall, the toxicity of nivolumab in the SQ NSCLC population was of less concern than that of docetaxel; only a few AEs (for example, dysphonia, hypercalcaemia and hypothyroidism) were more common for nivolumab, once adjusted for exposure. Much of the improvement in safety comes from the essential absence of neutropenia in patients given nivolumab.

In line with the patient population, dyspnoea and cough were reported more often than in melanoma patients. There is a discussion of 'cough' as an AE. To that can be added the observation from the MEL Supplementary clinical evaluation report of Study 067 that cough was reported as an AE in ~20% of patients in each arm. Overall, there is no consistent signal that nivolumab commonly causes coughing, although there is evidence that less commonly, it can cause pneumonitis (which would often present as coughing, dyspnoea, fever, etcetera).

In Study 003, 4/129 NSCLC patients died because of nivolumab related pneumonitis; in subsequent studies this problem seems to have abated, apparently because of earlier/more vigorous management of pneumonitis. So, in Study 017, only 3/131 subjects had a serious AE of pneumonitis, and only one of those three SAEs was grade 3-4.

Risk management plan (RMP)

Advice from the ACSOM is recorded in the Round 2 RMP report. A key observation in the RMP evaluation was that:

> *Given the clinical data suggest that combination therapy may be associated with significantly greater toxicity than nivolumab monotherapy, it is recommended that this observation be emphasised by the healthcare provider and patient communication tools to facilitate safe and effective use of nivolumab in post market use.*

The RMP Round 2 evaluation report states in relation to conditions of registration for the RMP:

> *At this time no wording can be provided, as it is recommended that an acceptably revised ASA be submitted before this application is approved.*

Negotiations between the sponsor and the TGA RMP Evaluation Section are ongoing as of 21 October 2015, for example, all communication tools have not been supplied for review yet.

Issues

Efficacy: melanoma

Nivolumab monotherapy is efficacious relative to dacarbazine (Study 066, in first line BRAF WT patients), ipilimumab (Study 067, in first line patients) and choice of chemotherapy (Study 037, after failure of IPI ± BRAF inhibitor; based on interim ORR data).

The clinical evaluator was not convinced of the clinical benefit of treatment beyond progression, because a survival benefit was not clear in such patients.

Nivolumab *in combination with ipilimumab* is efficacious relative to ipilimumab (Study 067; Study 069). It appears to have more efficacy than nivolumab alone, perhaps due to higher efficacy in patients with PD-L1 negative tumours. That is, in patients with PD-L1 positive tumours, there is no strong signal of a benefit over nivolumab, at least in terms of PFS.

Efficacy: melanoma – BRAF status

The US FDA has approved nivolumab monotherapy for patients with both BRAF WT and BRAF mutant tumours, but those with mutant tumours must have progressed following a BRAF inhibitor. This accelerated approval was on the basis of Study 037.

The FDA has approved combination therapy only in BRAF V600 WT patients. Approval, also accelerated, was based on Study 069. This study enrolled patients with BRAF V600 mutant melanoma, but 108/140 subjects were BRAF WT; and the primary endpoint was in BRAF WT patients.

In Study 067, the pivotal study for combination therapy, there were ~100 BRAF mutant patients per arm, versus ~215 per arm for BRAF WT. The primary endpoint was not specific to BRAF WT patients.

Actual outcomes varied by BRAF status as follows, for ORR (Tables 16-17).

Table 16. ORR by BRAF status.

ORR per investigator	BRAF WT		BRAF mutant	
↓ Arm. Study →	Study 069	Study 067	Study 069	Study 067
IPI	10.8%	17.7%	0% (0/10)	22% (22/100)
nivolumab	NA	46.8%	NA	36.7%
combination	59.7%	53.3%	43.5%	66.7%

Table 17. PFS by BRAF status.

Median PFS	BRAF WT		BRAF mutant	
↓ Arm. Study →	Study 069	Study 067	Study 069	Study 067
IPI	4.7 months	2.8 months	2.7 months	4.0 months
nivolumab	NA	7.9 months	NA	5.6 months
combination	8.9 months	11.2 months	7.4 months	11.7 months

In Study 037, in the nivolumab arm, ORR was 34% for WT, and 23% for mutant. (In the chemo arm, results were 11% and 9% respectively.)

In Study 066 (Phase III; versus dacarbazine; first line) only subjects with BRAF WT tumours were enrolled.

An important consideration is that there has been no direct comparison of the efficacy of nivolumab or combination therapy relative to targeted (BRAF inhibitor ± MEK inhibitor) therapies.

Possibly, nivolumab has more Anti-tumour efficacy in patients with BRAF WT tumours than in patients with BRAF mutant tumours (for example, results of Study 037 and of Study 067). However, in both studies (037; 067) involving nivolumab monotherapy and patients with BRAF mutant tumours, nivolumab had better efficacy than the comparator, in the BRAF mutant subset. The studies were not formally designed to address this issue.

Ipilimumab's indication is not limited by BRAF status; neither is pembrolizumab's.

Efficacy: SQ NSCLC

There is evidence of nivolumab's efficacy versus an appropriate comparator, docetaxel. The evidence is in patients who have progressed after first line, platinum based chemotherapy – but the proposed indication allows use after any first line chemotherapy.

The US PI states "patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA approved therapy for these aberrations prior to receiving Opdivo". Since most patients with EGFR and ALK aberrations do not have squamous cell NSCLC, this issue is less relevant for the current application than for the application to register use in patients with NSQ NSCLC.

Safety: monotherapy

The safety of nivolumab monotherapy has been well characterised in a series of trials against relevant comparators – dacarbazine (in first line, BRAF WT advanced melanoma patients); ipilimumab (in first line advanced melanoma patients); choice of dacarbazine or paclitaxel/carboplatin (in second/third line advanced melanoma patients) and docetaxel (in 2nd line advanced SQ NSCLC patients).

The type of AEs caused by nivolumab is in keeping with the type seen in clinical studies of other checkpoint inhibitors, that is, autoimmune type AEs affecting, most commonly, skin and gastrointestinal tract, less commonly the liver, endocrine organs (in particular the thyroid gland), kidneys and lungs, and rarely various other organs. The safety profile of nivolumab is more favourable than that of ipilimumab (see Study 067).

Safety: combination with ipilimumab

The safety of nivolumab in combination with ipilimumab has been well characterised in Study 067 and Study 069. There is a clear signal of a major increase in toxicity with the combined use of anti PD-1 and anti CTLA-4 mAbs. Pneumonitis, hepatitis, hypophysitis and similar potentially fatal AEs are all seen at a much higher frequency than with use of monotherapy nivolumab or ipilimumab. The high rate of significant AEs is in the setting of a clinical trial programme, that is, where exclusion criteria ensure patients with impaired organ function or known active autoimmunity are excluded, and where early treatment with corticosteroids is built into the study protocol. Therefore, the safety profile seen in Study 067 and Study 069 can arguably be considered a best case scenario.

- *Question for ACPM: Given the frequency of severe immune mediated AEs in patients with combination treatment, what clinical investigations (if any) should be recommended in the PI for monitoring, and how often should they be used, to increase the likelihood of early diagnosis? Should there be any different approach for monotherapy?*

In this regard, the most recently proposed PI recommends monitoring in very general terms. For example, in relation to pneumonitis: "Patients should be monitored for signs

and symptoms of pneumonitis such as radiographic changes (for example, focal ground glass opacities, patchy filtrates [sic]), dyspnoea, and hypoxia".

- *Questions for sponsor:*

  In key clinical trials, what clinical investigations were used in a monitoring role to detect AEs early, and how often were they used?

  Given the 5-6% usage of anti TNF mAbs to treat colitis in the combination arm of Study 067, are there trial data to inform about the effectiveness of this approach, when to move to anti TNF therapy, etcetera? Should such information be included in the PI (compared with Yervoy)?

Risk management plan

Many immune mediated AEs may progress in severity without early and vigorous use of corticosteroids and related management approaches, and there is a risk that the safety profile seen in Phase III studies will not translate into clinical practice if measures built into clinical trial protocols are not implemented in practice. The sponsor does note (in a response to questions in the supplementary clinical evaluation report, dated 14 October 2015):

> *Additional risk minimization will be provided by a HCP Immune-Related Adverse Reaction Management Guide and a Patient Alert Card. As the frequency of most immune related adverse reactions is increased with the combination of nivolumab and ipilimumab, BMS will ensure this point is reinforced in the above educational materials.*

(This response also attempts to address some concerns ACSOM had with Study 234, the post approval observational study of nivolumab in routine practice. Study 401 is also proposed to examine AEs with combination therapy, and it is proposed that 20 centres in Australia be included. This can only add to the familiarity with combination therapy issues in Australia.)

- *Question for ACPM: Are there any suggestions about how the RMP can be improved to increase patient safety with the combination approach?*

Risk-benefit analysis

Delegate's considerations

There is acceptable evidence of a positive benefit/risk balance for nivolumab in the following settings:

- Monotherapy use for treatment of patients with unresectable or metastatic melanoma; and
- Monotherapy use for treatment of locally advanced or metastatic SQ NSCLC with progression on or after prior chemotherapy

The remainder of this discussion focuses on benefit-risk balance with the combination approach.

The Delegate agrees with the clinical evaluator that value should be shown relative to monotherapy with nivolumab (*as well as* ipilimumab). If only combination therapy were proposed for use, the TGA adopted EU 'Guideline on the evaluation of anticancer medicinal products in man' has guidance:

> *If the experimental agent (A) is added to an established regimen (B), superiority of AB versus B should be demonstrated and benefit-risk should be shown to be*

> *favourable. A discussion is expected based on available data as regards dose intensity of B and benefit risk. Traditionally, this type of studies does not include an A alone third arm, but this should be justified based on available exploratory study data.*[44]

However, in this case, monotherapy (A, that is, nivolumab) is also proposed for registration, and it seems reasonable to require, in this case, that AB also provides an advantage over A. The sponsor provided its views on this subject in its response to the MEL Supplementary clinical evaluation report (dated 14 October 2015). IPI is an appropriate comparator within Study 067. A broader issue is whether the combination should be approved without demonstration of advantage over nivolumab monotherapy.

Relative to nivolumab monotherapy, there is a major step-up in toxicity with addition of ipilimumab to the regimen. Toxicity of the combination did not, however, contribute to patient deaths (at least directly, or as reported in Study 067). There is also a risk that, if clinical monitoring for early signs of immune-mediated ADRs is not intense, toxicity will be worse than was seen in clinical trials.

An increase in toxicity may impact on quality of life. Study 067 included QoL outcomes (EORTC-QLQ-C30). Nivolumab patients had slower decline in global health status than combination or IPI monotherapy patients.

In terms of efficacy, relative to nivolumab monotherapy which itself is efficacious:

- An ORR of ~60% (with a CRR of >11%) is a distinct advance.
- PFS outcomes are also impressive, with the suggestion of a benefit for combination relative to nivolumab monotherapy (for example, HR 0.74 [95% CI 0.60-0.92] in Study 067).

In the setting of good efficacy but major toxicity, OS outcomes provide an assurance that toxicity is not outweighing efficacy, at the study level.

The TGA adopted EU 'Guideline on the evaluation of anticancer medicinal products in man' divides treatments into those administered with curative intent, with the intent to achieve long term disease control, and with palliative intent.[45] Palliation is 'last line' so not applicable; in the other settings, in the circumstance of a major increase in toxicity, the principal objective should be to demonstrate improved survival. OS is a co-primary endpoint of Study 067, but OS data are immature. This might be an argument to defer approval until OS data are mature – but an (arguably) major PFS benefit has been seen, even relative to monotherapy with nivolumab.

Many patients had to discontinue the combination due to toxicity – this did not prevent the combination from having better efficacy overall, and there is a suggestion ORRs are higher in such patients.

A consideration is that efficacy of the combination relative to nivolumab monotherapy is not markedly improved (in terms of PFS) in patients with PD-L1 positive tumours. The efficacy benefit of combination therapy relative to nivolumab monotherapy resides in patients with PD-L1 negative tumours. It is difficult to approve an indication limited by PD-L1 status when no assay is widely available for this biomarker. The latest update about availability of an assay is as follows (from the sponsor's response to the MEL Supplementary clinical evaluation report, dated 14 October 2015):

> *BMS confirms that the PD-L1 IHC assay is planned to be marketed in Australia and will be submitted to the TGA by Dako/Agilent for regulatory approval by Nov-2015.*

[44] European Medicines Agency, "Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4)", 13 December 2012.
[45] European Medicines Agency, "Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4)", 13 December 2012.

The sponsor notes "limitations of the subgroup analysis in relation to the interpretation of these results…":

- The primary objective of CA209067 was not to test the treatment arms for efficacy by PD-L1 status
- CA209067 does not have adequate power to compare these subgroups to allow drawing a definitive conclusion

However, it is difficult to avoid concluding that in patients with PD-L1 positive tumours, the benefit-risk balance of combination nivolumab + ipilimumab is not as good as that of single agent nivolumab, with a big step-up in toxicity not offset by a minor increment in efficacy (OS data unavailable; no benefit in PFS; moderate ORR benefit).

Due to better efficacy (as measured by ORR and PFS, but not OS), there may be a benefit of combination therapy (over nivolumab monotherapy) in patients with PD-L1 negative tumours.

An option would be to approve combination use in these patients. This might encourage the sponsor to drive registration of an assay for tumour PD-L1 expression. On the other hand, until the assay was ready, this might encourage use of unvalidated or inaccurate testing, or encourage off label use. Alternatively, approval of combination use could be postponed until an assay became available, despite clinical trial evidence that allows a decision informed by PD-L1 status. Or, data could be provided in the clinical trials and/or Precautions sections of the PI about the variation in efficacy by subgroup, to allow a more informed decision by patients and clinicians, despite no assay. The proposed PI does include significant detail about efficacy in subgroups defined by tumour PD-L1.

- *Questions for ACPM*

  Does the ACPM support approval of Opdivo plus Yervoy for use in patients with unresectable or advanced melanoma, or in some other melanoma patient subset (e.g. patients with PD-L1 negative tumours)?

  How should the issue of PD-L1 tumour status be addressed in the PI, given there is no currently registered assay?

Proposed action

Summary of issues

Nivolumab is an anti PD-1 mAb (second in class after pembrolizumab) that acts by removing the brakes on Anti-tumour immunity (this mechanism of action also induces immune mediated AEs). Ipilimumab, approved as a single agent in advanced melanoma, is an anti CTLA-4 mAb that serves a similar function.

In the Delegate's opinion, there is a positive benefit-risk balance for nivolumab **monotherapy** in unresectable or metastatic melanoma and (as a second line agent) in SQ NSCLC.

- In melanoma, efficacy and safety have been established relative to dacarbazine in a first line setting (Study 066), ipilimumab in a first line setting (Study 067) and choice of chemotherapy in a second or third line setting (Study 037).
- In SQ NSCLC, efficacy and safety have been established relative to docetaxel in a second line setting (Study 017).

For the combination use of nivolumab and ipilimumab, proposed for unresectable or metastatic melanoma, the benefit-risk balance must factor in:

- Dramatic toxicity, relative to nivolumab monotherapy (and even relative to IPI monotherapy). Potentially fatal immune mediated adverse events (for example, colitis, pneumonitis, hepatitis, hypophysitis, rash) occurred often in Studies 067 and 069.
- The apparent need for intense clinical monitoring to diagnose and manage immune-mediated reactions at an early stage, to maintain the good record of reversibility and absence of fatal adverse drug reactions seen in the pivotal clinical trial for combination therapy.

Impressive efficacy, with caveats that (a) only in patients whose tumours were PD-L1 negative was the step up in efficacy (above and beyond that of *nivolumab* used as a single agent) compelling; and (b) there is no tumour PD-L1 assay currently available.

Request for ACPM advice

5. Does the ACPM support approval of Opdivo plus Yervoy for use in patients with unresectable or advanced melanoma, or in some other melanoma patient subset (for example, patients with PD-L1 negative tumours)?

If the ACPM supports use of the combination approach in any group:

6. Given the frequency of severe immune mediated AEs in patients with combination treatment, what clinical investigations (if any) should be recommended in the PI for *monitoring*, and how often should they be used, to increase the likelihood of early diagnosis? Should there be any different approach for monotherapy?
7. Are there any suggestions about how the RMP can be improved to increase patient safety with the combination approach?
8. How should the issue of PD-L1 tumour status be addressed in the PI, given there is no currently registered assay?
9. Is a 'Black-Box' warning along the lines of that in the Yervoy PI required?

In general:

10. Does the ACPM have any other advice relevant to this application, for example, concerning nivolumab monotherapy, or PI/CMI documents?

Pre ACPM preliminary assessment

Use as a monotherapy, as proposed by the sponsor, is acceptable.

Use in combination with ipilimumab, as proposed by the sponsor, is a more complex issue, as per above. The ACPM's advice is requested to help inform my view about the benefit-risk of this treatment option.

Response from sponsor

Introduction

The sponsor agrees with the Delegate and clinical evaluator's recommendation that there is a positive benefit/risk balance for nivolumab monotherapy in patients with unresectable or metastatic melanoma and as a second line agent in patients with SQ NSCLC.

The sponsor wishes to provide the following comments in support of the use of nivolumab and ipilimumab combination therapy (combination therapy) in patients with unresectable or metastatic melanoma.

Efficacy of combination therapy

The sponsor agrees with the Delegate that the evidence of efficacy meets the requirements of the TGA adopted EMA 'Guideline on the evaluation of anticancer medicinal product in man'[46] by demonstrating evidence of superior efficacy of combination therapy to the established immunotherapy, ipilimumab.

The Delegate noted that Study CA209067 demonstrated a distinct advance in terms of ORRs and impressive improvements in PFS, with the suggestion of a benefit for combination therapy relative to nivolumab monotherapy.

In Study CA209067, the addition of nivolumab to ipilimumab demonstrated significantly improved median PFS over ipilimumab alone in All Randomised subjects (11.5 months versus 2.9 months; HR 0.42 [95% confidence interval (CI): 0.31, 0.57]; P <0.0001). A descriptive analysis from Study CA209067 also provided evidence that combination therapy improved PFS when compared to nivolumab monotherapy (11.5 months versus 6.9 months; HR = 0.74 [95% CI: 0.60, 0.92]).

In both Studies CA209067 and CA209069, combination therapy demonstrated significantly higher ORRs compared with ipilimumab alone in All Randomised subjects (57.6% versus 19%; odds ratio: 6.11 [95% CI: 3.59, 10.38]; P<0.0001) and (55.8% versus 8.5%; odds ratio: 15.08 [95% CI: 4.85, 46.93]; P < 0.0001), respectively). Complete responses (CR) were observed in 11.5% of subjects with combination therapy compared with 2% with ipilimumab monotherapy in Study CA209067 and approximately 17% of subjects with combination therapy compared to 0% with ipilimumab monotherapy in Study CA209069.

The ORR and CR rates observed with combination therapy in Study CA209067 were higher than those for nivolumab monotherapy (ORR 58% versus 44% and CR 11.5% versus 8.9%).

Both nivolumab monotherapy and ipilimumab monotherapy have demonstrated an OS benefit in patients with unresectable or metastatic melanoma. In patients treated with ipilimumab monotherapy a median OS of 11.4 months with survival rates ranging from 20% to 26% with an apparent plateau in the OS curve around 3 years has been observed in patients followed up for 10 years.[47] Updated OS from subjects treated with nivolumab monotherapy in Study CA209066 based on 15.1 months of follow-up (representing an additional 11.3 months of follow-up since the primary analysis) demonstrated a clinically meaningful superior OS compared to dacarbazine (HR 0.43 [95% CI: 0.33, 0.57], P<0.0001) with a 24 month survival rate of 57.7% (95% CI: 49.7, 64.9) and median OS not yet reached.[48]

Exploratory data from the Phase II Study CA209069 in the All Randomized population at 11 months of follow-up showed OS rates of 73% and 66% in combination therapy and ipilimumab monotherapy arms, respectively; however, the median OS was not reached in either arm.

The choice of ipilimumab monotherapy as the formal comparator in Study CA209067 against the investigational arms was based on clinical acceptance of ipilimumab as the standard of care in the treatment of unresectable or metastatic melanoma as supported by

[46] European Medicines Agency, "Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4)", 13 December 2012.
[47] Schadendorf D, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. *J Clin Oncol* 33: 1889-1894 (2015).
[48] Addendum 02 to Final Clinical Study Report for Study CA209066 A Phase 3, Randomized, Double-blind Study of BMS-936558 (Nivolumab) Versus Dacarbazine in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma. Document Date 13-Oct-2015. DCN 930094841.

international guidelines. Nivolumab was not considered as a formal comparator as it was an investigational agent at the time Study CA209067 commenced on the 11 June 2013.

The US FDA recently granted accelerated approval for combination therapy for patients with BRAF V600 WT unresectable or metastatic melanoma based on the results from study CA209069. The sponsor confirms that Study CA209067 has been submitted to the FDA and is currently being evaluated under priority review.

These results demonstrate that combination therapy is a highly effective treatment regimen demonstrating significantly higher ORR, more frequent CRs, and significantly improved PFS compared to immunotherapy monotherapies.

PD-L1 subgroup analysis

The Delegate has posed questions to the ACPM in relation to the interpretation and clinical applicability of the subgroup analysis by tumour PD-L1 status. The exploratory analysis in study CA209067 was not adequately powered to compare these subgroups and therefore requires careful interpretation in the context of the overall study result.

In Study CA209069, PD-L1 subgroup analyses demonstrated that combination therapy provides a longer PFS and higher ORR irrespective of tumour PD-L1 expression levels (1%, 5%, and 10%) when compared to ipilimumab alone. A Cox proportional hazards model of PFS showed no significant interaction between PD-L1 status and treatment effect.

In Study CA209067, a longer PFS and higher ORR was observed in the nivolumab monotherapy and combination treatment groups regardless of PD-L1 expression status relative to the ipilimumab treatment group.

For subjects whose tumours had low to no PD-L1 expression (<1% and <5%), both a longer PFS and higher ORR was observed with combination therapy compared to nivolumab monotherapy.

However, for subjects who were positive for PD-L1 expression (≥1% and ≥5%), a higher ORR but a similar PFS was observed with combination therapy when compared to nivolumab monotherapy.

No differences in the frequencies of immune related adverse reactions (irARs) by PD-L1 expression subgroup (using either a 1% or 5% tumor PD-L1 expression level) were observed in any select irAR category across the treatment groups.

Combination therapy addresses a high unmet medical need for patients with advanced melanoma by providing a treatment option that produces deep and durable responses in a large proportion of patients. Although the greatest benefit for the combination versus nivolumab monotherapy may occur in the setting of low to no PD-L1 expression, clinically meaningful improvement in response rates were observed across all PD-L1 expression levels.

While the Opdivo PI can describe the results from this study, considerations from the individual patient perspective can only be incorporated via the clinical judgement of the treating physician with regard to clinical complexity, circumstance and the disease characteristics of the patient. For this reason, BMS considers that it is important that combination therapy is available to all patients with metastatic melanoma regardless of their PD-L1 expression levels. The results of the PD-L1 subgroup analysis from Study CA209067 should be described in the Opdivo PI so that oncologists can consider this information together with other patient characteristics when tailoring therapy on an individual patient level. Unlike testing for genetic mutations, expression of tumour PD-L1 is highly dynamic and may be variously expressed over time. Data on PD-L1 expression continues to rapidly evolve.

Whilst laboratory PD-L1 testing is currently available in Australia, BMS confirms that the PD-L1 IHC assay used in nivolumab clinical trials is planned to be registered in Australia and will be submitted to the TGA by Dako/Agilent for regulatory approval by the end of November 2015.

Identification and management of immune related adverse drug reactions

The sponsor acknowledges that subjects in the combination therapy arm of Study CA209067 experienced a higher rate of irARs compared with subjects in the ipilimumab and nivolumab monotherapy arms. However, management of these irARs through the use of treatment modification recommendations, algorithms for management, and use of immune modulatory medication resulted in resolution rates across select adverse reaction categories which were comparable to the nivolumab or ipilimumab monotherapy arms.

The sponsor agrees with the Delegate's comment that the safety of combination therapy has been well characterised. There were no unique adverse reactions attributed to the combination of nivolumab and ipilimumab that have not previously been seen with either agent alone.

No treatment related deaths were reported in subjects treated with combination therapy in Study CA209067.

Across select adverse reaction categories, the majority of these irARs resolved for patients receiving combination therapy, with the exception of endocrine adverse reactions. As has been observed in other nivolumab monotherapy studies, the majority of endocrine adverse reactions were not considered resolved because of the continued use of hormone replacement therapy and/or physiologic replacement doses of steroids. However, these were manageable and very few patients discontinued study therapy due to endocrine adverse reactions.

Resolution rates for select Grade 3 or 4 irARs in the combination therapy group were between 85 and 100% for most organ categories.[49]

The onset of most irARs with the combination therapy occurred during the initial combination phase rather than the maintenance phase with single agent nivolumab and typically occurred in a hospital setting where there is a high level of specialist patient care (median time to onset of all categories of irARs ranged from 0.5 months to 2.6 months).

The information provided on treatment resolution rates of irARs from studies CA209067 and CA209069 using established treatment algorithms, dosing interruption recommendations, and use of immunomodulatory therapies provides direct evidence that irARs associated with the use of combination therapy can be managed effectively.

The sponsor agrees with the Delegate that discontinuation did not prevent the combination from having better efficacy overall with a suggestion that ORRs are higher in such patients. In subjects who did discontinue combination therapy due to an irAR in study CA209067, 68% (81/120) experienced a complete or partial response. The median time to response was 2.8 months (−11.10.3), the median duration of response was 13.1 months (NA), ongoing responses among responders was 56/81 (69%) and. median PFS was 11.73 months (95% CI: 9.92, 16.72). Similar patterns of responses in patients who discontinued combination therapy were also observed in Study CA209069 with 68% (38/44) experiencing a complete or partial response. Median PFS in BRAF WT subjects was 8.57 months (95% CI: 7.03, NA).

[49] Postow M, et al. Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma. *N Engl J Med* 372: 2006-2017 (2015); Larkin J, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* 373: 23-34 (2015).

Translation of clinical trial AE management outcomes into clinical practice

The Delegate expressed concern that the safety profile observed in Phase III studies may not translate into clinical practice if measures built into clinical trial protocols are not implemented.

Clinical experience in identifying and managing irARs with ipilimumab treatment provides an established foundation for Australian oncologists to adopt new immunotherapies, such as the combination therapy, into clinical practice. Melanoma treating Australian clinicians have had several years of experience with ipilimumab since TGA approval in 2011 and PBS listing in August 2013. Approximately 230 oncologists across 153 Australian centres are listed as having used ipilimumab in the Australian Condition of Listing (ACOL) program. This experience has been extended to clinical trial use of combination therapy through involvement in Study CA209067 in which a total of 15 Australian investigators enrolled 116 Australian patients.

Through the availability of registered immunotherapies and clinical trial participation, Australian oncologists have developed expertise to identify and manage potential irARs associated with immunotherapy.

Hospital protocols for management of irARs and structured mechanisms for proactive patient follow-up following an immunotherapy infusion are now well established throughout melanoma treating centres in Australia. For available immunotherapies, the Cancer Institute NSW provides web based protocols for the use of these agents in the management of patients with advanced melanoma.

Education about immuno-oncology remains critical to the quality use of combination therapy. The sponsor's experiences with ipilimumab has developed the company's capability of implementing and delivering its education, clinical, product information and adverse effect awareness programs for combination therapy in a manner that:

- Increases awareness for the early identification of irARs in clinical practice and
- Improves the management of emergent irARs in clinical practice

The sponsor is providing additional support to oncologists to facilitate the translation of the clinical evidence to support combination therapy and management of irARs into clinical practice. These programs apply across the unit of care in oncology, including patients, nurses, pharmacy, and physicians and are described below.

- The RMP proposed by the sponsor contains risk minimisation activities which are designed to inform HCP of the important identified risks of irARs and the requirement for close monitoring, early diagnosis, and prompt and appropriate management. Routine risk minimisation is provided by the Opdivo PI. Additional risk minimisation will be provided by a HCP Immune-Related Adverse Reaction Management Guide (HCP tool) and a Patient Alert Card.

  The HCP tool will be an aid to ensure understanding of the immunologic aetiology of irARs and the requirement for frequent monitoring and/or immediate actions that need to be taken. Signs and symptoms for each body organ system of irARs will be described with detailed treatment algorithms for management. These treatment algorithms will be presented in a diagrammatic format which describes irARs by body organ system and severity. The treatment algorithms then provide clear guidance on action to be taken regarding nivolumab/ipilimumab (for example, withhold/discontinue) and specific recommendations in relation to the treatment of irARs (eg, corticosteriods or noncorticosteriod immunosuppressive medication). The sponsor will include a statement regarding the safety of the combination therapy that aligns with the PI.

The HCP tool will also include a reminder to distribute the Patient Alert Card and to educate patients/caregivers about signs and symptoms of irARs and of the need to report them immediately to their HCP provider.

The Patient Alert Card aims to educate patients in simple language on the signs and symptoms for each category of irARs and to assist patient and/or caregiver to identify and report irARs. The Patient Alert Card will warn patients about the risk of irARs and how to recognise the symptoms and to contact their HCP immediately if these occur or worsen.

The Patient Alert Card instructs the patient to bring to the attention of other treating healthcare practitioners (for example, emergency physician, dentist) that the patient is receiving immunotherapy and provides contact details of the patient's oncologist. The sponsor proposes to align this tool to reflect the combination therapy safety information as per the CMI.

- Australian oncologists will also be eligible to participate in the following two international studies to be conducted in Australia, which aim to build upon their established clinical experience with immunotherapy in managing patients with metastatic melanoma and capture relevant safety information on the use of nivolumab, including combination therapy, in routine practice.
  - CA209234 (Pattern of Use and Safety/Effectiveness of Nivolumab in Routine Oncology Practice) is being conducted internationally with a plan to include 80 centres to recruit 1200 patients (400 advanced melanoma and 800 NSCLC patients). Australia is a participant of this international program.
  - CA209401 (Clinical Trial of Nivolumab Combined with Ipilimumab Followed by Nivolumab Monotherapy as First-Line Therapy of Subjects with Histologically Confirmed Stage III (Unresectable) or Stage IV Melanoma) is being conducted internationally and includes 20 Australian centres with a plan to recruit 5 patients per centre.
- Clinical Networks for Medical Oncologist to Support the Use of Immunotherapies

  The sponsor manages a peer-to-peer clinical network in Australia to support medical oncologists in the safe and appropriate use of immunotherapy as well as to share experience and expertise. This program involves leading oncologists experienced in the use of immunotherapy for the treatment of metastatic melanoma who are available for referral on clinical matters relating to the use of immunotherapy to other oncologists around Australia. Their professional advice is independent and not directed by the sponsor. The program currently includes 7 leading Australian oncologists who are mentors to 27 medical oncologists on patient management with immunotherapy. The number of oncologists invited to participate in the peer-to-peer clinical support network is not capped and is planned to be expanded following the registration of nivolumab.

  The sponsor also provides sponsorship to support a two day clinical preceptorship program aimed at ensuring the quality use of immunotherapy. This particular program currently focuses on the management of patients with metastatic melanoma. This program is made available to all medical oncologists and melanoma oncology nurses from every state and territory through a leading cancer institution in Australia. The medical content of these preceptorships are independently developed by the institute running this program. Sponsorship of similar preceptorships are currently planned with the other hospitals and institutions in Australia to broaden access across Australia.

Product information

To support the early identification and appropriate management of potential irARs associated with combination therapy the sponsor agrees with the Delegate's recommendation to include a boxed warning for combination therapy in the Opdivo PI. To further augment this statement and to ensure that use is limited to oncologists who are experienced and appropriately trained in the use of immunotherapy, the sponsor proposes the following additional statement:

> *It is recommended that the combination of Opdivo and Yervoy should be administered and monitored under the supervision of physicians experienced with the use of immunotherapy in the treatment of unresectable or metastatic melanoma.*

To address the Delegate's question to the ACPM on what clinical investigations should be recommended in the Opdivo PI for monitoring to increase the likelihood of early diagnosis of irARs the sponsor proposes to include more directive recommendations for liver function and serum creatinine tests prior to and during treatment. Further responses to suggestions made by the TGA are provided in the sponsor's comments on the PI.

Conclusion

Despite the availability of approved treatments for metastatic melanoma there is strong medical and patient support for the use of nivolimab/ipilimumab combination therapy as an option to individualise treatment for patients with varying clinical circumstances and degrees of clinical complexity (submissions from the Medical Oncology Group of Australia and Melanoma Patients Australia to the Pharmaceutical Benefits Advisory Committee are provided).

The clinical evidence submitted with this application demonstrated that the combination of nivolumab and ipilimumab was superior in efficacy to ipilimumab in a broad patient population. A descriptive analysis of combination therapy compared to nivolumab monotherapy also provides evidence of superior efficacy. The types of adverse events reported with combination therapy were consistent with previous experience with nivolumab monotherapy and ipilimumab monotherapy; no new safety signals were identified with combination therapy.

Both combination therapy studies provide measurable outcomes from the management of adverse effects in terms of time to onset, time to resolution, and time to resolution in subjects who received immunemodulating medications.

Adverse reaction resolution rates measured across the nivolumab melanoma development program indicate comparable rates of success in subjects treated with nivolumab monotherapy to subjects treated with combination therapy. Of the patients who discontinued combination therapy due to an irAR approximately 68% displayed evidence of antitumour responses.

Based on the medical expertise developed by Australian oncologists through their participation in clinical trials of combination therapy and subsequent post registration usage of ipilimumab in clinical practice, immune related adverse reactions associated with combination therapy are manageable and translatable into Australian clinical practice. Recognising the need for continuous education and clinical experience with any new treatment, the activities proposed by the sponsor will assist oncologists in building upon their established experience in treating patients with immunotherapy, and provide support for identifying and managing adverse events associated with the combination of nivolumab and ipilimumab.

Key irAR management algorithms and treatment interruption recommendations utilised in the combination studies submitted with this application have been incorporated into the proposed Opdivo PI. More specific directions designed to enhance the detection and management of irARs have also been added in the form of a boxed warning with a

recommendation that treatment should only be initiated by physicians with prior experience in the use of immunotherapeutic agents. All of the above is also reflected in the additional risk minimisation tools for HCPs.

Metastatic melanoma continues to be an aggressive and potentially fatal disease despite the emergence of new therapies. The addition of combination therapy represents an important alternative to allow Australian clinicians treating melanoma the ability to individualise therapy when considering treatment options for patients with varying clinical circumstances and degrees of clinical complexity.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Opdivo concentrate solution for IV infusion containing 10 mg/mL of nivolumab to have an overall positive benefit-risk profile for the amended indication;

> *Opdivo, as monotherapy is indicated for the treatment of patients with unresectable or metastatic melanoma.*
>
> *Opdivo, in combination with Yervoy (ipilimumab) is indicated for the treatment of patients with metastatic melanoma with elevated lactic dehydrogenase (LDH) or M1c disease.*
>
> *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*

In making this recommendation, the ACPM:

- Was of the view that combination treatment for metastatic melanoma could be restricted to patients with poor prognosis that is, patients with elevated LDH or M1c disease.

Proposed conditions of registration

The ACPM agreed with the delegate on the proposed conditions of registration.

PI/ CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- Advice in the PI that clinical parameters such as electrolytes, urea and creatinine (EUC), liver function tests (LFTs), thyroid function tests (TFTs), blood sugar levels (BSL), amylase and cortisol should be monitored 2 to 3 weekly in the induction phase and every 4 weeks in the maintenance phase (metastatic melanoma combination therapy).
- A 'Black Box' warning similar to Yervoy.
- Carfeul and clear explanation of the toxicities of combination treatment with nivolumab and ipilimumab in metastatic melanoma in the CMI.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does the ACPM support approval of Opdivo plus Yervoy for use in patients with unresectable or advanced melanoma, or in some other melanoma patient subset (for example, patients with PD-L1 negative tumours)?*

The ACPM acknowledged that there is increased toxicity with combination therapy, but despite this patients derive benefit from treatment. The ACPM was of the view that combination therapy with nivolumab and ipilimumab has a role in the treatment of patients with poor prognosis who generally do not respond well on treatment with ipilimumab or nivolumab monotherapy. This poor prognosis group can be identified by elevated LDH or M1c metastatic melanoma. The indication for combination therapy could be limited to these patients as they are likely to derive the most benefit.

The ACPM also advised that treatment should not be limited by PD-L1 status as more data are required to inform this issue. In addition, there is no validated test available and this would likely become a major issue for prescribers.

2. *Given the frequency of severe immune mediated AEs in patients with combination treatment, what clinical investigations (if any) should be recommended in the PI for monitoring, and how often should they be used, to increase the likelihood of early diagnosis? Should there be any different approach for monotherapy?*

The ACPM advised that regular frequent blood tests be undertaken in the induction phase such as 2 to 3 weekly, measuring parameters such as EUC, LFTs, TFTs, BSL, amylase and cortisol. During the maintenance phase, monitoring at 4 weekly intervals would seem appropriate. Routine imaging should not be necessary except on presentation of symptoms.

3. *Are there any suggestions about how the RMP can be improved to increase patient safety with the combination approach?*

The ACPM advised that it is not necessary to restrict prescribing to specialised groups as this may create access issues. However, patients prescribed combination therapy should have access to experienced and well trained clinicians because of the toxicity of the regimen.

4. *How should the issue of PD-L1 tumour status be addressed in the PI, given there is no currently registered assay?*

The PD-L1 tumour status should not be specified as there are insufficent data at present to support stratification of treatment by PD-L1 status. This could be modified at a later date where more data are provided.

5. *Is a 'Black-Box' warning along the lines of that in the YERVOY PI required?*

The ACPM advised that a 'Black Box' warning is appropriate similar to the YERVOY PI.

6. *Does the ACPM have any other advice relevant to this application, e.g. concerning nivolumab monotherapy, or PI/CMI documents?*

The ACPM advised that based on the available data it is possible that nivolumab has more anti-tumour efficacy in patients with BRAF WT tumours than in patients with BRAF mutant tumours (for example, results of Study 037 and of Study 067). However, in both studies involving nivolumab monotherapy and patients with BRAF mutant tumours, nivolumab had better efficacy than the comparator in the BRAF mutant subset. The ACPM noted that the studies were not formally designed to address this issue. The ACPM also noted that the indications for ipilimumab and pembrolizumab are not limited by BRAF status. Therefore, treatment should not be limited by BRAF status, and clinical judgement should be allowed.

The ACPM also advised that the CMI should ensure that the toxicities with combination treatment are explained very clearly.

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

IX. Concurrent submission: NSQ NSCLC

The initial submission for Opdivo was considered by the ACPM with the following proposed indications:

> *Opdivo, as monotherapy is indicated for the treatment of patients with unresectable or metastatic melanoma.*
>
> *Opdivo, in combination with Yervoy (ipilimumab) is indicated for the treatment of patients with metastatic melanoma with elevated lactic dehydrogenase (LDH) or M1c disease.*
>
> *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*

A concurrent submission was then submitted to the TGA, with the following proposed indication:

> *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.*

The second submission was considered by a clinical evaluator and TGA Delegate, but was not considered by ACPM.

Clinical

Introduction

Non squamous non-small cell lung cancer (NSQ NSCLC)

Lung cancer is classified as small cell and non-small cell lung cancer (NSCLC; this comprises ~85% of lung cancers). The WHO histological classification of NSCLC is:

- Squamous cell carcinoma (25% of lung cancers; ~31% of NSCLC) ("SQ NSCLC").
- Adenocarcinoma (40% of lung cancers; ~50% of NSCLC).
- Large cell carcinoma (10% of lung cancers; ~13% of NSCLC).
- Other (≤5% of lung cancers; ~6% of NSCLC)

These histological subtypes arise in different anatomical compartments, for example, SQ NSCLC may often arise from the central airway compartment (so may arise close to large vessels, etcetera). There are further histological divisions within the adenocarcinoma subtype.

As well as histology, key influences on the choice of initial therapy for advanced disease are:

- extent of disease (for example, number and site of metastases);
- presence of symptoms related to a specific metastatic site;
- presence of driver mutations (for example, EGFR; ALK; ROS1); and

- the patient's overall condition and co-morbidities

Influences on the choice of subsequent therapy for advanced disease are similar. Another influence is choice of prior treatment (that is, the need for a non cross resistant approach).

It is generally considered that treatment of advanced NSCLC aims to prolong survival and maintain quality of life, while minimising side effects of treatment, that is, there is a palliative focus. Further, almost all patients with advanced NSCLC eventually develop progressive disease that requires additional treatments.

Historically, patients with NSQ NSCLC had better outcomes and more acceptable treatment options than patients with squamous NSCLC (this was used to explain the sponsor's approach of pursuing SQ and NSQ NSCLC indications separately).

Pemetrexed is only indicated in locally advanced or metastatic NSCLC "other than predominantly squamous cell histology". Bevacizumab's NSCLC indication is restricted to NSQ NSCLC. Likewise, afatinib's approval is restricted to use in non squamous disease. Therefore, there are more treatment options in NSQ NSCLC. In particular, there is the choice of pemetrexed (instead of docetaxel) for patients who have progressed after treatment with a platinum based approach, although this might not apply if pemetrexed has been used as part of initial therapy.

The sponsor's initial submission to register nivolumab, dated 6 January 2015, requested approval for use in advanced melanoma. Based on the sponsor's summary of outcomes in a Phase III study in SQ NSCLC ("Study 017"), the TGA allowed the scope of the submission to enlarge to include SQ NSCLC. That application is yet to be decided.

The current submission for use in NSQ NSCLC is separate.

There is a further submission being considered, for use of nivolumab in a subset of patients with renal cell carcinoma.

Pembrolizumab is another mAb in the same class, that is, an anti-PD-1 mAb. It was registered in April 2015 for use in advanced melanoma. A study of pembrolizumab in NSCLC has been published.[50]

Overseas regulatory history

USA: FDA

Nivolumab is registered in the US with the following indications:

> ***Unresectable or Metastatic Melanoma***
>
> *Opdivo (nivolumab) as a single agent is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor [see Clinical Studies (14.1)].*
>
> *This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.*
>
> *Opdivo, in combination with ipilimumab, is indicated for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma [see Clinical Studies (14.1)].*
>
> *This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.*

[50] Garon EB, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med.* 372: 2018-28 (2015).

Metastatic Non-Small Cell Lung Cancer

Opdivo (nivolumab) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo [see Clinical Studies (14.2)].

Initial approval dated 22 December 2014 was accelerated approval as a single agent in patients with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

The stipulated trial commitment is described as follows:

Conduct and submit the results of a multicentre, randomized trial or trials establishing the superiority of nivolumab over standard therapy in adult patients with unresectable or metastatic melanoma who are refractory to ipilimumab or who have not been previously treated with ipilimumab.

The scheduled final report submission was 31 December 2016.

Subsequently there was standard approval for metastatic SQ NSCLC dated 4th March 2015. The application was not referred to an FDA advisory committee. The FDA determined that a study was needed in the post market setting to assess immune mediated adverse reactions, including immune mediated pneumonitis; the condition is as follows:

Conduct a randomised trial that will characterize the incidence, severity and response to treatment of nivolumab induced immune-mediated adverse reactions to include immune-mediated pneumonitis.

The study's final report is scheduled for submission on 31 December 2015. The sponsor has explained that Study 017 fulfils this requirement (RMP Round 2 Evaluation page 8).

There was also a post marketing commitment as follows:

Submit the final report and efficacy datasets for the open-label randomized trial of nivolumab versus docetaxel in patients with previously treated advanced squamous non-small cell lung cancer.

This study's final report was also scheduled for submission on 31 December 2015.

Lately, there has been accelerated approval for use in combination with ipilimumab in melanoma dated 30 September 2015.

As outlined in the FDA approval letter, accelerated approval was on the undertaking to conduct and submit for evaluation a clinical trial. The stipulated trial commitment is described as follows:

Conduct and submit the results of a multicentre, randomized trial or trials to verify and describe the clinical benefit of nivolumab in combination with ipilimumab in previously untreated adult patients with unresectable or metastatic, BRAF V600 wild-type melanoma.

The scheduled final report submission is 31 July 2015, that is, apparently this should already have been submitted; the trial may refer to Study 067 (which is in a broader patient group, that is, not restricted to patients with BRAF WT tumours).

Most recently, there has been approval for NSQ NSCLC (the indication was merged with the existing SQ NSCLC indication, with addition of restrictions in patients whose tumours have EGFR or ALK tumour genomic aberrations). The approval letter required the conduct of a study of immune mediated encephalitis, as follows:

> *An Enhanced Pharmacovigilance Study to evaluate the risks factors and clinical sequelae of immune-mediated encephalitis following exposure to Opdivo (nivolumab). This study will include a mechanism to collect, classify, and analyse data on moderate to severe neurologic deterioration in patients exposed to Opdivo (nivolumab).*

An interim report is due at the end of 2017; a final report is due at the end of 2021.

EU: EMA

In the EU, nivolumab (as Opdivo or Nivolumab BMS) is approved for the following indications:

> *Opdivo as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. [authorised 16.6.2015]*

and

> *Nivolumab BMS is indicated for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults. [authorised 20.7.2015]*

With regard to nivolumab in melanoma, a requirement for marketing authorisation was provision of physician educational materials and patient alert cards. There was also an obligation to submit:

- the final study report for Study 037, by 30 June 2016, and
- updated OS data for Study 066, by 31 December 2015.

There was a further requirement to explore the value of biomarkers.

With regard to nivolumab in SQ NSCLC, a requirement for marketing authorisation was provision of physician educational materials and patient alert cards. There was also an obligation to submit updated OS data for Study 017, by 31 December 2015. There was a further requirement to explore the value of biomarkers, as per above for Opdivo.

The combination with ipilimumab has not yet been approved in the EU.

Contents of clinical dossier

Study 057 (pivotal) and Study 003 (supportive) have been considered in this review of nivolumab's use in NSQ NSCLC.

Pharmacokinetics

Studies providing pharmacokinetic data

Study 057 had as an exploratory endpoint, the characterisation of the PK of nivolumab and exploration of exposure-response relationships. This characterisation is the subject of a separate report, entitled "Nivolumab Population Pharmacokinetics and Exposure-Response Analyses in Subjects with Previously Treated Squamous or Non-Squamous Non-Small Cell Lung Cancer" (report dated 20 June 2015). As suggested by the title, the report considers both SQ and NSQ NSCLC.

Previous Population PK analyses of nivolumab have been conducted as follows:

- Population PK Report dated 26 May 2014 (n = 669 patients) focusing on NSCLC patients in Study 003 and Study 063
- Population PK Report dated 18 July 2014 (n = 909)
- Population PK Report dated 8 December 2014 (n = 1110)
- Population PK Report dated 23 April 2015 (n = 1314)

The report dated 23 April 2015 included data from Study 057 (amongst other studies, as detailed in the TGA Clinical Evaluation Report for nivolumab in squamous NSCLC). While that report was based on analysis of n = 1314 subjects, it focused on exposure-response outcomes in patients with squamous NSCLC.

The report dated 20 June 2015 includes the same population PK modelling as was included in the report dated 23 April 2015.

On the other hand, the report dated 20 June 2015 includes exposure-efficacy (OS) analyses in patients with SQ NSCLC, and separately, NSQ NSCLC. Exposure-safety analyses were conducted after pooling across SQ and NSQ patients.

Thus, the exposure-efficacy (OS) analysis of patients with SQ NSCLC in this synoptic report was the same as that shown in the report dated 23 April 2015. However, the exposure-efficacy analysis of patients with NSQ NSCLC is 'new' information, as is the exposure-safety analysis. These analyses are considered below.

Evaluator's overall conclusions on PK

There was no sign of any dramatic difference in the PK of nivolumab in patients with NSQ NSCLC, relative to other studied patient groups.

A correlation between nivolumab exposure and efficacy has not been ruled out (see above). Also, an influence of baseline serum albumin level (presumably a surrogate for various conditions that may influence nivolumab PK) on nivolumab exposure has not been ruled out.

There was little focus on the potential relationship between dose interval (for example, Q2W versus Q3W) and efficacy or safety outcomes.

Pharmacodynamics

No new PD data have been considered in this evaluation report.

Dosage selection for the pivotal studies

The CSR for Study 057 notes that:

> *The nivolumab dose regimen of 3 mg/kg Q2W evaluated in this study was chosen based upon an interim analysis on 24-Feb-2012 of safety, efficacy, and exposure-response data from approximately 300 subjects treated in the Phase 1 study CA209003 (also known as MDX1106-03). The results of exposure-response analyses showed that the probability of a tumour response tended to approach a plateau for trough concentrations produced by 3 mg/kg and 10 mg/kg administered Q2W. Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose tested, and no maximum tolerated dose was identified. The nature, frequency, and severity of drug-related AEs (including pulmonary select AEs), SAEs, AEs leading to discontinuation, and deaths were similar in NSCLC subjects across dose levels and histologies, as compared to the overall study population.*

Study CA209003 has been evaluated in the Clinical Evaluation Report for the application to register nivolumab for use in squamous NSCLC. The focus of that evaluation was evidence of efficacy / safety in the squamous NSCLC population. Exposure-response analyses for nivolumab have been considered in Section 4.2 of that CER, again with a focus on squamous NSCLC. The ~300 subjects referred to by the sponsor above are a heterogeneous group of patients, including patients with NSCLC, melanoma, renal cell carcinoma and colorectal and prostate cancers. Comments about selection of dose regimen copied above appear reasonable. For the NSCLC group in Study 003, ORRs were 3% for 1 mg/kg, 24% for 3 mg/kg and 20% for 10 mg/kg, and this pattern held for both SQ and NSQ subgroups, although it did not extend to OS outcomes. The sponsor's conclusions copied above remain valid despite this possible threshold effect.

Efficacy

Evaluator's conclusions on clinical efficacy for NSQ NSCLC

Nivolumab provides a survival advantage over docetaxel in NSQ NSCLC patients who have failed initial platinum based therapy AND whose tumours are PD-L1 positive. This is also reflected in PFS and ORR advantages.

In NSQ NSCLC patients who have failed initial platinum based therapy and whose tumours are PD-L1 negative, there is no advantage in survival over docetaxel, but no strong sign of detriment. There were imbalances in use of subsequent therapies (for example, docetaxel in the nivolumab arm) that may have contributed to this outcome. PFS outcomes in this group are mixed (for example, median PFS is higher with docetaxel; 12 month PFS rate is higher with nivolumab). Objective response outcomes favour docetaxel. In this group, with evidence of no survival advantage, analysis suggests no quality of life advantage with nivolumab.

While PD-L1 subgroup analyses are clearly relevant in NSQ NSCLC, other subgroup analyses of efficacy are also notable. For example, as a group, patients with EGFR mutations did not appear to share in the OS benefit (and this was not, it seems, due to any interaction with tumour PD-L1 status). Also, efficacy outcomes were strongly influence by geographic region (potentially due to baseline imbalances across arms in the 'Rest of world' group). Finally, the 'never smokers' group did not have a clear OS benefit. This finding superficially accords with views about nivolumab's mechanism of action.

In summary, there is ample evidence of good efficacy (relative to docetaxel) for nivolumab in NSQ NSCLC patients who have failed initial platinum based therapy AND whose tumours are PD-L1 positive (using a 1%, 5% or 10% threshold) AND whose tumours are not EGFR mutation positive. In others, the evidence for efficacy is less clearcut. There is no strong signal of any harm conferred by nivolumab in these other patients. Finally, there are too few subjects with ALK mutations to understand the benefit-risk balance of second line nivolumab in such subjects.

Safety

Patient exposure

In Study 057, the primary population for safety analysis was all treated subjects (n = 287 for nivolumab, and 268 for docetaxel). There were 156.7 person-years of exposure to nivolumab, and 95.5 PYs for docetaxel.

Safety issues with the potential for major regulatory impact

Liver toxicity

While nivolumab appears to cause LFT derangements, there was not a strong signal for dangerous hepatotoxicity, with only occasional severe derangements.

Haematological toxicity

Beyond significant suppression of absolute lymphocyte counts in ~12% of subjects (a lower percentage than for docetaxel), there was not a strong signal for haematological toxicity. Grade 4 falls in platelet counts were reported in two nivolumab subjects.

Serious skin reactions

Rash and pruritus were common, but serious reactions (for example, those reported as grade 3-4) were uncommon (2/287 nivolumab patients).

Cardiovascular safety

There is no signal of direct cardiovascular toxicity with nivolumab, although it can be presumed that autoimmune events such as myocarditis will occur, probably uncommonly. Other toxicities (for example, diarrhoea causing dehydration; pneumonitis causing hypoxia; etcetera) could have as their sequelae cardiovascular events.

Unwanted immunological events

Hypersensitivity

The frequency of hypersensitivity or infusion related reactions was 3.5% for nivolumab and 5.2% for docetaxel patients. There were no reports of anaphylaxis, although bronchospasm was reported in 3 subjects (~1%) per arm (none of the nivolumab cases were thought to be drug related).

Immunogenicity

Study 057 had as an exploratory endpoint characterisation of nivolumab's immunogenicity. In the nivolumab arm (n = 251 with baseline and at least 1 post baseline result), 7.2% were positive at baseline for ADAs, while 17.1% (n = 43) were ADA positive on study. No subject was persistently positive, but 12/43 subjects were positive for the last sample tested and 3 subjects had neutralising antibodies. One of these three subjects also reported drug related thyroiditis/hypothyroidism, over 2 months after neutralising ADAs were noted. 2/43 ADA positive subjects (4.7%) versus 6 out of >200 ADA negative subjects (<3.0%) had hypersensitivity or infusion site reactions. Survival times for the patients with neutralising antibodies were good (7.5, 23.9 and 24.1 months).

Version 0.8 of the nivolumab PI refers to an analysis of immunogenicity data pooled across various studies. The studies were 037, 063, 066, 017, 057 and 067 (monotherapy only). This pooled analysis relies on what is said to be an improved assay, ICDIM 140 V1.00/V2.02. The analysis as presented relies somewhat on assertion, for example, regarding the 9 subjects with neutralising antibodies, "the safety profiles of these 9 subjects were examined and determined to be no different than those observed in ADA negative subjects". Overall, the text proposed in the PI regarding this topic is reasonable.

Immune related AEs

General comments

The sponsor defined various categories of 'select AE', that is, AEs of special clinical interest, very broadly overlapping with 'immune related AEs' (for example, requiring corticosteroids for management, or whose early recognition and management may mitigate severe toxicity). These are discussed below.

The sponsor also characterised 'immune mediated AEs' (pneumonitis, diarrhoea/colitis, hepatitis, nephritis/renal dysfunction, rash and endocrine events). These overlap with 'select AEs', although immune mediated AEs were limited to subjects who received immunosuppressive medicines to treat the event (except in the case of endocrine AEs).

Diarrhoea/colitis

Gastrointestinal select AEs were reported in 15.7% of nivolumab subjects but 27.2% of docetaxel subjects. In the nivolumab arm, there were two subjects with grade 3 events (a subject with grade 3 diarrhoea and colitis; another with grade 3 diarrhoea). Median time to onset of any drug related GI select AE was 4.7 weeks. Five subjects required high dose corticosteroids. One subject received infliximab. In 21/22 cases of drug related GI select AEs, events resolved (with median time to resolution of 1.5 weeks). An additional serious AE of grade 3 colitis was reported in extended follow-up (between 30 and 100 days after the last dose). Among nivolumab subjects reporting diarrhoea (45/287 or 15.7%), 14/45 had >1 event.

Hepatitis

There was routine monitoring of LFTs prior to each dose. Hepatic select AEs were reported in 10.1% of nivolumab subjects versus 2.6% of docetaxel subjects. Grade 3-4 hepatic select AEs were also more prominent with nivolumab (2.8% versus 0.7%). There was resolution in 11/15 cases. A case of grade 4 transaminitis was 'ongoing' as of the database lock (this subject died after sudden onset of respiratory insufficiency due to massive pleural effusion, associated with severely deranged LFTs, within 5 days of the 1st dose of nivolumab). In two nivolumab cases, there was drug related hyperbilirubinaemia. Another case was notable in that an initial grade 3 AST increase (at 33.7 weeks) resolved with high dose corticosteroids after 4 weeks (and dose delay), but re-challenge resulted in further hepatotoxicity resulting in treatment discontinuation.

Pneumonitis

Pulmonary select AEs were reported in 3.8% of nivolumab subjects (all were consistent with a pneumonitis like process) versus 1.1% of docetaxel subjects. Of note, grade 3 drug related pneumonitis or interstitial lung disease was seen in 4 nivolumab subjects; these events were all serious AEs and all led to discontinuation. Median time to onset in the 4 subjects was 27.5 weeks. All four patients received high-dose corticosteroids, and 3/4 events resolved. An additional report of pneumonitis was received in extended follow-up.

Nephritis/renal dysfunction

Renal select AEs were reported in 5.6% of nivolumab patients and 1.1% of docetaxel subjects. Most events were considered unrelated to study drug, however there were seven reports of nivolumab-related renal impairment/failure (versus 1 docetaxel related report).

Endocrine events

Endocrine select AEs were reported in 10.8% of nivolumab subjects versus 1.1% of docetaxel subjects. Most events in the nivolumab arm were hypothyroidism, with some reports of hyperthyroidism. There was an AE of adrenal insufficiency in each study arm, and an AE of diabetes mellitus in each study arm; in the nivolumab arm neither AE was considered drug related. Median time to onset for endocrine select AEs was 12.1 weeks. Many events were not considered resolved, because of ongoing use of hormone replacement therapy. No AE of hypophysitis was reported.

Rash

Skin select AEs were reported in 26.5% of nivolumab subjects and 18.3% of docetaxel subjects. Most events were thought to be drug-related. In the nivolumab arm, there were two grade 3 events, but all others were grades 1-2 and no drug related events were

serious or led to discontinuation. 40/51 subjects (78.4%) with drug related events had resolution; 14 subjects used immune modulating medicines. Median time to onset of drug-related events was 5.1 weeks (the range was wide), but median time to resolution was 12.1 weeks.

Relationship between immune-related AEs and efficacy

In correspondence from the sponsor dated 13 August 2015, the sponsor presented landmark analyses of OS from month 4, 6, 8 and 12 by prior occurrence of any select adverse event. There was no compelling signal of a relationship, although it is noted that the point estimate for the HR (OS) consistently favoured 'prior occurrence' (magnitude of HR, ~0.8), at least suggesting no clear OS harm in patients who reported select AEs.

Evaluator's overall conclusions on clinical safety

Nivolumab's safety in this patient group has been reasonably well characterised, although for the dose likely to be proposed for use, that is, 3 mg/kg Q2W, there is large reliance on Study 057. Nivolumab is, overall, better tolerated than docetaxel. Much of the difference comes from the profoundly lower frequency of neutropenia with nivolumab, but there are other benefits (for example, a basic absence of alopecia, and lower rates of some other important AEs such as diarrhoea and stomatitis). On the other hand, nivolumab does cause immune mediated AEs, prominent examples being skin related events such as pruritus and rash, as well as diarrhoea (uncommonly, colitis), hepatitis (uncommonly including hyperbilirubinaemia), pneumonitis, nephritis and hypo and hyper thyroidism. These immune mediated AEs may be very well managed in a clinical trial context, and a risk is that in the community setting, clinicians and patients will have fewer prompts to manage early signs of such AEs appropriately. It is also important to understand whether the moderate signal of a different safety profile in patients with positive versus negative PD-L1 status is real or not – given the clear difference in efficacy across these groups, this will influence benefit / risk balance. Study 057's safety findings were broadly consistent with the safety profile of nivolumab seen in other settings.

First round benefit-risk assessment

First round assessment of benefits

The benefits of nivolumab in the treatment of NSQ NSCLC patients who have failed platinum based doublet chemotherapy (and tyrosine kinase inhibitor therapy in relevant subjects) are, relative to docetaxel:

- A clear OS benefit in PD-L1 positive subjects (who constitute about half of studied subjects), consistent with advantages in PFS and ORR outcomes in this sub-group.
- The prospect of meaningful survival gains in a higher fraction of patients than is seen with docetaxel.
- An overall better safety profile, in large part because nivolumab does not induce neutropenia (whereas docetaxel commonly causes profound neutropenia), but also because nivolumab does not cause other important toxicities seen with docetaxel (for example, alopecia), or causes them less frequently (for example, diarrhoea, stomatitis).

First round assessment of risks

The risks of nivolumab in the treatment of NSQ NSCLC patients who have failed platinum-based doublet chemotherapy (and tyrosine kinase inhibitor therapy in relevant subjects) are, relative to docetaxel:

- Apparently less frequent objective responses coupled with more frequent early disease progression in patients whose tumours are PD-L1 negative. This is offset by the absence of any sign of OS detriment, in PD-L1 negative subjects.

- The possibility of worse efficacy outcomes in patients whose tumours are EGFR mutation positive. In the case of patients whose tumours are ALK mutation positive, there are insufficient data to understand benefit-risk very clearly.
- The possibility that in other subgroups (for example, the elderly, or 'never smokers') the efficacy benefits of nivolumab relative to docetaxel may not materialise.
- The occurrence of immune mediated adverse reactions, akin to autoimmune events, which can be severe and/or persistent, and even fatal, despite the close monitoring for and early management of such events in the clinical trial context. In the community context, where such monitoring and management may be less stringent, immune mediated adverse reactions of significance could be more common. This implies the need for considerable investment in risk mitigation measures, for example, tailored education.

First round assessment of benefit-risk balance

The benefit / risk balance is positive for this use of nivolumab in patients whose tumours are PD-L1 positive and EGFR WT.

In patients whose tumours are PD-L1 positive but EGFR mutant, benefit-risk is less clear.

In patients whose tumours are PD-L1 negative, benefit-risk is also unclear. There is no indication that OS is worse in such patients who receive nivolumab compared to such patients who receive docetaxel. Anti-tumour responses are better with docetaxel in this group (although duration of response in nivolumab responders is encouraging). This must be balanced against the better safety profile of nivolumab (there is even a weak signal that in PD-L1 negative patients, nivolumab related AEs may be less frequent than in PD-L1 positive subjects, although the sponsor does not consider there to be any particular difference in this regard).

Availability of a validated PD-L1 assay is of interest given the above assessment. The sponsor notes that:

> *…a validated PD-L1 assay utilised in the BMS studies will be made available in Australia through our diagnostic partner Dako/Agilent. A device application to register the biomarker test is planned to be submitted to the TGA by Dako/Agilent.*

First round recommendation regarding authorisation

The clinical evaluator recommends approval of nivolumab for use in NSQ NSCLC, but with a modified indication:

> *Opdivo, as monotherapy is indicated for the treatment of locally advanced or metastatic non squamous non-small cell lung cancer (NSCLC) in patients with progression on or after chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, Opdivo should be used after progression on or after targeted therapy.*

This approach to patients with tumour EGFR or ALK genomic aberrations is in line with entry criteria for Study 057, that is, such patients used nivolumab as a third line agent. There was no signal that efficacy was improved with nivolumab (relative to docetaxel) in such patients; the recommendation for inclusion of such patients in the indication is on the basis of better safety, resulting in a possibly acceptable benefit-risk balance. However, this is a somewhat grey area, since the HR for OS in patients with EGFR mutations was 1.18 favouring docetaxel (95% CI 0.69-2.00).

An alternative approach would be to exclude these patients from the indicated use, although targeted therapeutic options for patients progressing after initial targeted therapy for EGFR or ALK mutated tumours are unavailable in Australia currently.

It is also noted that the proposed indication, and the indication recommended above, make reference to progression on or after 'chemotherapy' whereas in Study 057, patients had failed platinum doublet based chemotherapy.

The clinical evaluator also recommends that the PI make very clear the distinct variation in efficacy outcomes seen in NSQ NSCLC patients depending on tumour PD-L1 expression, for example, within the Clinical Trials section of the PI. Suitable text is already proposed.

Delegate's considerations

Background

FDA approved indications of nivolumab are:

> *Opdivo is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of:*
>
> *Unresectable or metastatic melanoma:*
>
> - *as a single agent in patients with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.*
> - *in combination with ipilimumab in patients with BRAF V600 WT melanoma. These indications are approved under accelerated approval based on tumor response rate and durability of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in the confirmatory trials.*
> - *Metastatic non-small cell lung cancer in patients with progression on or after platinum based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA approved therapy for these aberrations prior to receiving Opdivo.*
> - *Advanced renal cell carcinoma in patients who have received prior antiangiogenic therapy.*

The Delegate notes that following the registration of the NSQ NSCLC indication, the FDA has mandated:

> *An Enhanced Pharmacovigilance Study to evaluate the risks factors and clinical sequelae of immune mediated encephalitis following exposure to Opdivo (nivolumab). This study will include a mechanism to collect, classify, and analyse data on moderate to severe neurologic deterioration in patients exposed to Opdivo (nivolumab).*

The FDA has approved the Dako pharmDX PD-L1 assay for companion use with pembrolizumab, and not in conjunction with nivolumab.

The EMA has approved the following indication:

> *Nivolumab BMS is indicated for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.*

The targets and mechanism of actions are described in the clinical overview for the initial submission.

Quality

The dose form and strength is unchanged from that proposed in the initial submission. There were no outstanding issues precluding registration for the initial submission.

No new data was presented for evaluation.

Nonclinical

There were no outstanding issues precluding registration for the initial submission.

No new data was presented for evaluation.

Clinical

Pharmacology

An update to the population pharmacokinetic model previously compiled was submitted. Exposure estimates were available from 347/354 patients recruited to the two NSQ NSCLC efficacy studies.

The modelling reported exposure-response findings for both efficacy and safety. The variables associated with a significant effect on OS were: baseline ECOG status, PD-L1 status, line of treatment, nivolumab clearance, body weight and baseline LDH.

Variables associated with a significant effect on risk of nivolumab discontinuation were: >2 lines of prior therapy, baseline ECOG status >0, decreased baseline albumin and increased baseline LDH.

The Delegate notes the conclusion of the clinical evaluator that

> *There was no sign of any dramatic difference in the PK of nivolumab in patients with NSQ NSCLC, relative to any other studied patient groups.*

Efficacy

Two clinical studies were presented for evaluation:

Study 057 (pivotal)

An open label, Phase III study that randomised previously treated advanced or metastatic non-squamous NSCLC patients to nivolumab or docetaxel.

The primary objective was the assessment of OS. Secondary objectives were ORR, PFS, evaluation of PD-L1 as a predictive biomarker for OS and ORR, and evaluation of symptomatic improvement using the Lung Cancer Symptom Scale.

The study was conducted across 106 sites in 22 countries, commending in November 2012. The database lock of 18 March 2015 was used, at a pre-planned interim analysis point.

Patients were required to have either Stage IIIB or Stage IV disease, or had recurrent or progressive disease following multimodal therapy. Of note, patients with EGFR mutations or ALK translocations who had disease progression after the use of a tyrosine kinase inhibitor AND platinum-based doublet chemotherapy (in either order) were permitted.

Randomised treatment was either nivolumab at the proposed dose of 3 mg/kg every 2 weeks, or docetaxel, at the currently registered dose of 75 mg/m2 every 3 weeks. Randomisation was stratified for prior maintenance therapy and second versus third line of therapy. Appropriate dose reductions or delays were permitted. Treatment continued until disease progression or unacceptable toxicity.

Baseline characteristics were consistent with the wider population with advanced/metastatic NSQ NSCLC, and were generally balanced, with the majority being Caucasian and

Tumour PD-L1 status was assessed by “using a rabbit anti-human PD-L1 antibody (clone 28-8; Epitomics Inc, Burlingame, CA US) to assess PD-L1 expression in archived pre-study

(baseline) FFPE tumour samples from the subjects in this study". PD-L1 expression could be: missing (no available specimen); quantifiable (that is, available specimen + at least 100 viable cells per Dako IHC assay + a call on the percentage of PD-L1+ cells); indeterminate (that is, unquantifiable, with staining hampered due to biology of specimen); or not evaluable (that is, unquantifiable due to suboptimal collection or preparation of the specimen).

For patients assigned to nivolumab 292 were randomised and 290 were assigned docetaxel; assigned treatment was received in 287 and 268 patients respectively.

Exposure to study therapy was longer in the nivolumab arm (>6 months in 30.3%) as compared to docetaxel (>6 months in 14.2%).

Consistent with the known effects of docetaxel, patients in this arm were more likely to have received concomitant G-CSF stimulants and pre-medication steroids. The use of systemic steroids for AEs was commoner in the nivolumab arm.

The primary outcomes of the study was met – HR for OS was 0.73 (95% CI 0.59 to 0.89) in favour of nivolumab, with a median OS of 12.2 months for nivolumab and 9.4 months for docetaxel, and a 12 month OS rate of 50.5% versus 39.0%.

Among those subjects with quantifiable PD-L1 status positivity was associated with an increase in survival. However, there is a substantial proportion of missing data in each treatment arm – 20.9% in the nivolumab arm and 22.8% of the docetaxel arm had non-quantifiable PD-L1 status. The HR of OS for those patient groups with either negative, or non-quantifiable, PD-L1 status was no different between the two treatment arms.

Despite the difference in hazard of OS being in favour of nivolumab, PFS was not significantly different between the treatment arms (HR 0.92, 95% CI 0.77-1.11). The sponsor has presented the PFS outcomes according to PD-L1 status however the bias associated with the large proportion of missing data also pertains to this outcome assessment.

Overall ORR was higher in the nivolumab arm, with four patients receiving nivolumab having a complete response as compared to one patient in the docetaxel arm.

Compliance with quality of life assessments was insufficiently complete to categorically confirm a non-deleterious effect of one treatment over the other. For those patients that did complete QoL assessments, outcomes were comparable between treatment arms.

Study 003 (supportive)

This was a Phase I, open label, dose escalation study of nivolumab in subjects with various advanced or recurrent malignancies.

This study recruited patients with advanced or recurrent malignancies, having had 1-5 lines of prior therapy and no remaining curative options.

Seventy four patients with NSQ NSCLC received nivolumab at doses of either: 1, 3 or 10 mg/kg (patients with other tumours received additional dosage levels).

Partial responses were observed for 13/74 (17.6%) NSQ NSCLC patients, no patients had a complete response. Median duration of survival was 10 months and median PFS was 1.9 months. The proportion surviving over time was similar between patients with NSQ and SQ NSCLC.

Safety

Safety in Study 057 was assessed in those patients that received the allocated study drug.

The most commonly occurring adverse events occurring irrespective of relationship to study treatment in the nivolumab arm were fatigue (31.7%), decreased appetite (28.9%),

cough (26.5%), constipation (23%), dyspnoea (22.6%), nausea (22%) and asthenia (20.6%).

The clinical evaluator notes:

> *the safety profiles of nivolumab and docetaxel are quite distinct, in that nivolumab is not often associated with alopecia (nivolumab, 1.4%; docetaxel, 26.1%), neutropenia (0.7% versus 32.5%, with a similar imbalance in related terms) or febrile neutropenia (0% versus 11.2%).*

Events occurring less commonly in the nivolumab arm, with a an incidence of at least 10% difference included: diarrhoea (15.7% versus 27.2%), anaemia (11.8% versus 25.4%), mucosal inflammation (2.1% versus 7.8%), stomatitis (2.1% versus 9%), peripheral neuropathy (3.1% versus 9.3%), dysgeusia (2.4% versus 10.1%), skin erythema (2.1% versus 6.7%) and 'lacrimation increased' (1.0% versus 8.2%). With nivolumab, there is more musculoskeletal pain (13.6% versus 4.5), pruritus (11.5% versus 1.9%) and hypothyroidism (6.6% versus 0%).

When adjusted for duration of exposure, the overall rate of adverse events was lower in the nivolumab arm (1745 AEs per 100 person-years) than docetaxel (2862 AEs/100 P-Y).

Overall, there were fewer TEAEs in the nivolumab arm. However, some 'select AEs' considered treatment related were more common in the nivolumab arm than the docetaxel arm, for example, endocrine select AEs (9.4% for nivolumab, 0.4% for docetaxel); hepatic AEs (5.2% versus 1.9%); pulmonary AEs (3.5% versus 0.4%); renal AEs (2.4% versus 0.4%); and skin AEs (17.8% versus 13.1%)

Deaths and SAEs

The proportion of deaths occurring in Study 057 was consistent with the severity of the underlying stage of disease: 185/287 (64.5%) of nivolumab subjects had died, versus 204/268 (76.1%) of docetaxel subjects. Within 30 days of the last dose of study drug, 12.5% versus 7.8% of subjects had died, respectively.

One patient in the nivolumab arm died as a result of encephalitis which was study drug associated. Four additional SAEs of headache and two of confusional state were reported in nivolumab exposed patients.

The comparative difference in SAEs included febrile neutropenia (0% for nivolumab, 9% for docetaxel); malignant neoplasm progression (8.0% versus 2.6%); pneumonia (4.2% versus 4.9%); pulmonary embolism (3.8% versus 1.1%); dyspnoea (3.1% versus 1.9%); pleural effusion (2.8% versus 1.1%); respiratory failure (2.1% versus 1.5%); and neutropenia (0% versus 3.0%). Also relevant is pneumonitis as an SAE (1.4% [i.e. 4/287] versus 0%), and interstitial lung disease (0.7% versus 0%). Given the fatal AE of encephalitis linked to nivolumab, it is relevant 'mental status changes' was reported as an SAE in 0% versus 1.1%.

A smaller proportion of patients receiving nivolumab discontinued therapy due to AEs, however there were differences in the proportion of events between the treatment arms, with fatigue/asthenia and malignant disease progression being commoner reasons for nivolumab exposed patients as compared to peripheral oedema and peripheral neuropathy being commoner among the docetaxel exposed patients.

Laboratory tests

Bilirubin and liver transaminase elevations occurred more commonly among the nivolumab exposed patients. Of note, elevations of ALT or AST of up to 20x ULN were reported.

Concurrent pneumonitis and hepatotoxicity were observed in one patient.

Thyroid function derangement was observed in 18.7% of nivolumab patients as compared to 2.9% of those receiving docetaxel. The majority had high TSH (12% versus 2.4% respectively) as compared to low TSH (6.7% versus 0.5% respectively).

Absolute lymphocyte count was reduced in 13.2% of nivolumab patients.

For serum calcium, 2 patients had grade 3 elevation in the nivolumab arm; none occurred in the docetaxel arm.

Hyponatraemia of grade 3 and 4 occurred in 7% and 1.4% of nivolumab patients respectively as compared to 4.2% and 0% of docetaxel patients. All four patients with grade 4 hyponatraemia had concomitant conditions to account for the derangement.

Serious AEs included febrile neutropenia (0% for nivolumab, 9% for docetaxel); malignant neoplasm progression (8.0% versus 2.6%); pneumonia (4.2% versus 4.9%); pulmonary embolism (3.8% versus 1.1%); dyspnoea (3.1% versus 1.9%); pleural effusion (2.8% versus 1.1%); respiratory failure (2.1% versus 1.5%); and neutropenia (0% versus 3.0%). Also relevant is pneumonitis as an SAE (1.4% [that is, 4/287] versus 0%), and interstitial lung disease (0.7% versus 0%). Given the fatal AE of encephalitis linked to nivolumab, it is relevant 'mental status changes' was reported as an SAE in 0% versus 1.1%.

Immunological events

The frequency of hypersensitivity, or infusion related reactions, was comparable between nivolumab and docetaxel patients.

Anti-nivolumab antibodies were observed in 7.2% at baseline and 17.1% post baseline samples in the nivolumab arm of study 057; in three patients, the ADA was described as neutralising. The duration of survival for the three patients ranged from 7.5 to 24.1 months.

Diarrhoea/colitis was reported for two nivolumab patients (each grade 3). Among 22 cases of drug related GI AEs, 21 events resolved. Of 45 patients reporting diarrhoea as an AE, 33% had a recurrence.

Pneumonitis was reported in 3.8% of nivolumab patients as compared to 1.1% of docetaxel patients. Grade 3 pneumonitis/interstitial lung disease was seen in 4 nivolumab patients, all of which were serious events and resulted in discontinuation.

Nephritis was reported in 5.6% of nivolumab patients and 1.1% of docetaxel subjects. Most events were considered unrelated to study drug, however there were seven reports of nivolumab-related renal impairment/failure (versus 1 docetaxel related report).

No events of hypophysitis were reported.

RMP evaluation

The Delegate is not seeking ACPM advice regarding the RMP.

Discussion

Efficacy

In patients with locally advanced or metastatic NSQ NSCLC who had received at least two prior therapies, the use of nivolumab was associated with a statistically significant reduction in hazard of death, as compared to patients receiving docetaxel. A difference in median OS of 3.5 months was observed, in favour of nivolumab.

Patients in Study 057 were not stratified according to PD-L1 status. The magnitude of HR of OS for the patients with non quantifiable PD-L1 status in Study 057 does not demonstrate a benefit from nivolumab. These patients do not necessarily fall into the PD-L1 negative category and thus may adversely affect the observed relationship with

survival in those with known, positive, status. The sponsor is not proposing to indicate the degree of PD-L1 expression as a determinant for patients to receive nivolumab therapy within the proposed indication.

The substantial proportion of patients in each treatment arm of study 057 without evaluable PD-L1 status is a major source of bias. The effect of this bias has not been discussed by the sponsor, and no sensitivity analysis has been conducted. It is noted that this study used archived tissue samples to assess PD-L1 status; the effect of sample age on ability to determine PD-L1 status has not been discussed. Given the large magnitude of missing PD-L1 data of >20% from patients in both treatment arms of Study 057, the true difference in duration of survival associated with PD-L1 status cannot be satisfactorily determined from the data presented. Although there were pre-specified levels of PD-L1 expression to be tested, the magnitude of missing data affects the powers of the trial to demonstrate the effect of degree of PD-L1 expression on survival. As per the TGA adopted EMA Guideline on Missing Data in Confirmatory Clinical Trials:[51]

> *It is not possible to establish the relationship between missingness and the unobserved outcome variable.*

There cannot be any extrapolation/imputation of data from patients with known PD-L1 status to those with unknown status.

This secondary outcome of Study 057 can thus only be considered an exploratory subgroup analysis as it cannot confirm the utility of the biomarker as a predictive tool; a further study satisfactorily reporting PD-L1 status results is required.

The Delegate further notes the advice of ACPM for the initial submission in regard to the proposed PI:

> *The PD-L1 tumour status should not be specified as there are insufficient data at present to support stratification of treatment by PD-L1 status. This could be modified at a later date where more data are provided.*

It is noted that the sponsor has stated:

> *A device application to register the biomarker test is planned to be submitted to the TGA by Dako/Agilent.*

Safety

In general, the safety profile of nivolumab in patients with NSQ NSCLC is not substantially different from that in patients with SQ NSCLC (considered approvable by the Delegate for that submission).

The comparative safety profile of nivolumab and docetaxel shows substantial differences in the pattern and severity of AEs, given the mechanism of action of each agent.

The Delegate notes the advice of ACPM from the initial submission to include a black box warning for the combination of nivolumab and ipilimumab. Following assessment of the NSQ NSCLC submission, there is no additional risk warranting the broadening of the black box warning.

Conditions of registration

The sponsor should present the results of the enhanced pharmacovigilance study of immune related encephalitis, mandated by the FDA, to the TGA when available.

[51] European Medicines Agency, "Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99)", 2 July 2010.

Proposed regulatory action

The Delegate considers that the demonstration of an improvement in OS in among the whole population of pivotal Study 057 associated with nivolumab exposure is sufficient to permit registration of the indication:

> *Opdivo, as monotherapy is indicated for the treatment of locally advanced or metastatic non squamous non-small cell lung cancer (NSCLC) in patients with progression on or after chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, Opdivo should be used after progression on or after targeted therapy.*

Given that the proposed PI for the NSQ NSCLC indication also contains the information pertaining to the melanoma and squamous NSCLC indications, the approval for the NSQ NSCLC indication will necessarily have to follow that for the other indications which are currently undecided.

X. Outcome

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

> *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*

Specific conditions of registration applying to these goods

- The EU RMP for Nivolumab (Version: 3.0, dated 19 June 2015), as qualified by the ASA (Version: 2.2, dated 18 December 2015), or any updates as agreed with the TGA, must be implemented in Australia.
- It is a condition of registration that, as a minimum, the first five independent batches of:
  - Opdivo (nivolumab) 100 mg in 10 mL (10 mg/mL) concentrate solution for IV infusion, vial
  - Opdivo (nivolumab) 40 mg in 4 mL (10 mg/mL) concentrate solution for IV infusion, vial

  imported into/manufactured in Australia are not released for sale until samples and the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratory Branch.

  The sponsor should supply:
  - Certificates of Analysis of all active ingredient (drug substance) and final product.

- Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
- Evidence of the maintenance of registered storage conditions during transport to Australia.
- 5 vials of each batch for testing by the TGA Laboratory Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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