Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Nivolumab

Proprietary Product Name: Opdivo

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

October 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

Common abbreviations

Abbreviation	Meaning
ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
AE-DC/D	Adverse event leading to discontinuation or death
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
CD4+	Activated helper T cells
CD8+	Activated cytotoxic T cells
CER	Clinical Evaluation Report
cHL	Classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMI	Consumer Medicine Information
CNS	Central nervous system
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DHCP	Dear Healthcare Professional
EMA	European Medicines Agency
ESMO	European Society of Medical Oncology
EU	European Union
FDA	Food and Drug Administration (US)
FKSI-DRS	Functional Assessment of Cancer Therapy-Kidney Symptom Index Disease-Related Symptoms scale
GCP	Good Clinical Practice
HCP	Healthcare professional

Abbreviation	Meaning
HR	Hazard ratio
HuMAb	Human monoclonal antibody
IL-	Interleukin-
IMAE	Immune mediated adverse event
irAE	Immune related adverse event
irAR	Immune related adverse reaction
IV	Intravenous
K-M	Kaplan-Meier
KPS	Karnofsky performance status
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MODS	Multiple organ dysfunction syndrome
MOF	Multiple organ failure
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	Mammalian Target of Rapamycin
NBE	New Biological Entity
NCCN	National Cancer Care Network
NCI	National Cancer Institute
NR	Not reached
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PBRER	Periodic Benefit Risk Evaluation Report
PBS	Pharmaceutical Benefits Scheme
PD-1	Programmed cell death-1 (receptor)

Abbreviation	Meaning
PFS	Progression free survival
PI	Product Information
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
QOL	Quality of life
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk Management Plan
SAE	Serious adverse event
SCCHN	Squamous cell cancer of the head and neck
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
TEN	Toxic epidermal necrolysis
TGA	Therapeutic Goods Administration
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New Biological Entity[1]
Decision:	Approved
Date of decision:	16 November 2016
Date of entry onto ARTG	18 November 2016
Active ingredient:	Nivolumab
Product name:	Opdivo
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd PO BOX 1080 Mount Waverly, VIC, 3149
Dose form:	Concentrate solution for injection
Strengths:	40 mg in 4 mL (10 mg/mL); and 100 mg in 10 mL (10 mg/mL)
Container:	Glass vial
Pack size:	1 vial per pack
Approved therapeutic use:	*Opdivo as monotherapy is indicated for the treatment of patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy in adults.*
Route of administration:	Intravenous infusion
Dosage:	Recommended dose of Opdivo as monotherapy is 3 mg/kg administered intravenously (IV) 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.
ARTG numbers:	231867, 231868

Product background

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

> *'the treatment of patients with advanced renal cell carcinoma (RCC).'*

Opdivo is already approved for the following indications:

> *'As monotherapy for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma*

1 This application can be seen as an extension of indication. It was submitted as a new biological entity (NBE) for administrative purposes prior to the initial decision for the first nivolumab application, to facilitate earlier review of the data.

In combination with Yervoy (ipilimumab) for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH).

As monotherapy for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy

As monotherapy for the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, OPDIVO should be used after progression on or after targeted therapy.'

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

Nivolumab is an immune checkpoint inhibitor. It is a fully human anti-PD-1 monoclonal antibody (mAb) of the immunoglobulin G4 isotype (IgG4) produced by recombinant DNA technology. It binds to programmed cell death-1 (PD-1) receptor on cells of the immune system and blocks the interaction between PD-1 receptor and its ligands, PD-L1 and PD-L2. Expression of PD-1 ligands occurs on the cells of some tumour types and signalling through this pathway can contribute to inhibition of active T cell immune surveillance of tumours. By inhibiting the PD-1 receptor from binding to PD-L1 and PD-L2, nivolumab reactivates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates anti-tumour immunity. Nivolumab is a 'second in class' to be approved for use in Australia. Pembrolizumab, another anti-PD-1 mAb, was approved by the TGA in April 2015 for use in advanced melanoma.

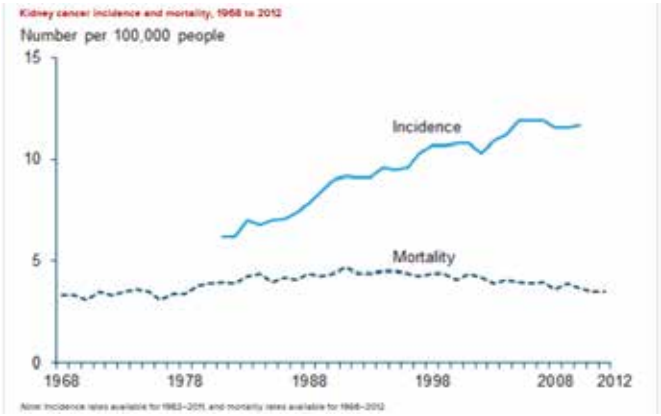
Therapeutic indication

Renal cell carcinoma (RCC) accounts for approximately 90 to 95% of neoplasms arising from the kidney. Several different types of RCC are now recognised, according to histological appearance, chromosomal alterations and molecular pathway abnormalities, with clear cell RCC accounting for 70 to 80% of cases.[2]

Kidney cancer in Australia

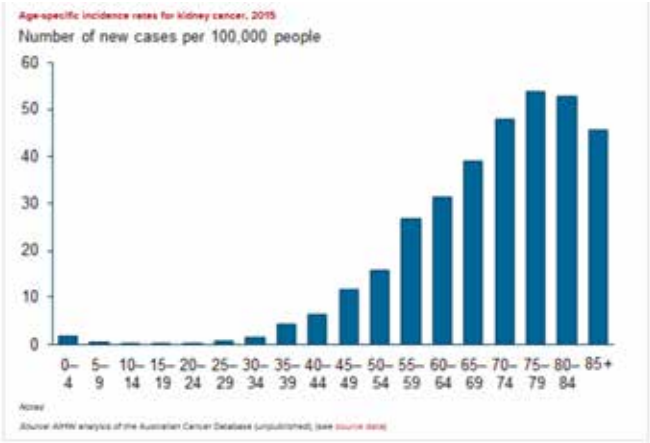
The overall incidence of kidney cancer in Australia has been increasing since 1978. Kidney cancer is more common in males and the incidence rate generally increases with age, up to the age group of 75 to 79 years, as shown below in Figures 1 and 2.[3]

Figure 1. Incidence and mortality of kidney cancer in Australia (1968 to 2012)



2 Escudier B et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology 25 (Supplement 3): iii 49–iii 56, 2014.
3 Cancer Australia (website) based on Australian Institute of Health and Welfare data.

Figure 2. Age specific incidence rates for kidney cancer in Australia (2015)



In 2011, there were 2,847 new cases of kidney cancer diagnosed in Australia (1,861 males and 985 females) and the age standardised incidence rate was 12 cases per 100,000 persons (16 for males and 7.7 for females). At the end of 2009, there were 9,627 people living who had been diagnosed with kidney cancer in the previous 5 years. In 2012, there were 907 deaths from kidney cancer in Australia, giving an age-standardised mortality rate of 3.5 deaths per 100,000 persons (4.9 for males and 2.3 for females). In 2007 to 2011, individuals with kidney cancer had a 73% chance of surviving for 5 years, compared to their counterparts in the general Australian population.

Diagnosis and prognosis

RCC is characterised by a lack of early warning signs, diverse clinical manifestations and resistance to radiation and chemotherapy. More than half of RCCs are currently detected incidentally due to the increasingly widespread use of abdominal imaging for example, ultrasonography, computed tomography and magnetic resonance imaging.

RCC may be cured if diagnosed and treated while it is still localised to the kidney and surrounding tissue. After radical nephrectomy for Stage I RCC, the 5 year survival rate is approximately 94%. Patients with Stage II lesions have a survival rate of 79%. When distant metastases are present or if any treated RCC patient develops progressing, recurring or relapsing disease, the prognosis is poor with 5 year survival rates of 0 to 20%.

Treatment options

Surgical resection is the standard of care for Stage I to III RCC and may be curative.

There is no curative therapy for Stage IV or metastatic disease. Surgical resection and/or metastasectomy may be considered in suitable patients to relieve symptoms and decrease ectopic hormone or cytokine production. Because some RCC have a very indolent course, a period of observation before starting treatment may be considered, especially in patients with limited tumour burden and few symptoms. For some poor prognosis patients, best supportive care may be the most appropriate treatment option.

Systemic treatment of renal cell carcinoma is rapidly evolving. Prior to 2005, the widely used systemic agents were the cytokines, interferon alfa and interleukin-2, which yielded modest efficacy and substantial toxicity although some patients achieved durable complete responses with interleukin-2. Molecularly targeted therapies have been developed in the last 10 years and have demonstrated significant activity in advanced stage RCC, such that they have displaced cytokine therapy. Currently available targeted therapies are made up of two broad classes; anti-vascular endothelial growth factor (VEGF) agents that act via inhibition of the VEGF pathway and inhibitors of the

mammalian Target of Rapamycin (mTOR) kinase signalling within tumour cells causing cell cycle arrest, enhanced apoptosis and inhibition of angiogenesis.

Despite these new therapies, outcome of progressive disease after first-line therapies remains poor, with median overall survival less than 2 years.[4]

Targeted therapy and immunomodulatory agents are now considered standard of care in patients with metastatic disease, although optimal regimens have not been identified. Most commonly, first line therapy is with a vascular endothelial growth factor receptor (VEGFR) kinase inhibitor. At disease progression, options include another type of angiogenesis-targeted therapy or 'switching the mechanism of action' to an mTOR inhibitor (for example everolimus). Interleukin-2 in high dose may still be used alone in some selected patients.

A number of options for first and second line therapies are suggested in the available guidelines, including the European Society of Medical Oncology (ESMO) Renal Cell Carcinoma Clinical Practice Guideline and the United States (US) National Cancer Institute (NCI) National Cancer Care Network (NCCN) guideline. There is no evidence that any particular follow-up protocol affects outcome in early or advanced RCC. The NCCN guideline states that follow-up should be individualised according to the patient's requirements. The ESMO guideline recommends: '*During systemic therapy in mRCC patients, 2 to 4 month follow-up schemes with CT scan should be advised to determine response and resistance. Although not perfect, RECIST criteria remain the best method to assess drug efficacy.*' The RECIST criteria is given below in Table 1.

Table 1. Response Evaluation Criteria in Solid Tumours (RECIST)

Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows:
Complete response (CR) is disappearance of all target lesions.
Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.
Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.
Stable disease (SD) is small changes that do not meet above criteria

TGA Approved Therapies (as of March 2016)

Therapies currently available in Australia for advanced RCC are in keeping with the guidelines described above and are shown below in Table 2. Agents approved for first line use are sunitinib, pazopanib, sorafenib and temsirolimus. Agents approved for second line use are axitinib and everolimus.

Table 2. Targeted therapies approved for use in advanced renal cell carcinoma in Australia

Active substance(s)	Approved Indication
Bevacizumab in combination with interferon alfa-2a	Treatment of patients with advanced and/or metastatic renal cell cancer

4 Quinn D et al. Renal-Cell Cancer: Targeting an Immune Checkpoint or Multiple Kinases. N Engl J Med 2015; 373:1872-1874.

Active substance(s)	Approved Indication
Sunitinib[1]	The treatment of advanced renal cell carcinoma
Pazopanib[1]	The treatment of advanced and/or metastatic renal cell carcinoma
Sorafenib[1]	The treatment of patients with advanced renal cell carcinoma
Temsirolimus	The treatment of advanced renal cell carcinoma
Axitinib[1]	The treatment of patients with advanced renal cell carcinoma after failure of one prior systemic therapy
Everolimus[1]	The treatment of advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib
[1)] PBS funded for stage IV clear cell variant renal cell carcinoma with strict clinical criteria	

Axitinib and everolimus are funded by the Pharmaceutical Benefits Scheme (PBS) for 'Stage IV clear cell variant' RCC provided the patient has progressive disease according to RECIST following first-line treatment with a tyrosine kinase inhibitor (TKI) and has a World Health Organization (WHO) performance status of 2 or less.

Checkpoint inhibitors including nivolumab

The complexity of tumour interaction with the human immune system is not fully understood.[5] Current thinking is that malignant tumour progression and growth may occur through mechanisms that enable tumour cells to evade detection and destruction by the immune system. One of these mechanisms involves cell-surface expression of one or more of a series of molecules that effectively limit T cell proliferation and killing capacity. These molecules are referred to as 'immune checkpoints' and their natural function is to restrain or dampen excessive immune responses.

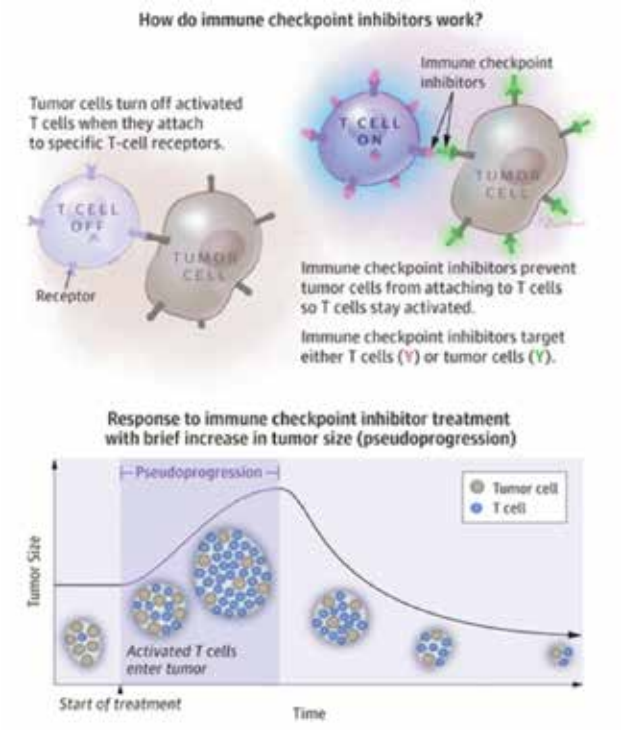
One such checkpoint is the interaction between the programmed cell death ligands (PD-L1 and PD-L2) and the PD-1 receptor that may be found on T and B lymphocytes. PD-L1 and PD-L2 are proteins that are normally expressed on macrophage-lineage cells, although expression of PD-L1 can be induced on other haematologic cells. Upon antigen recognition, activated T cells express PD-1 on their surface and produce interferons that lead to the expression of PD-L1 in multiple tissues. Binding of PD-1 to its ligands inhibits effector T cell activity and protects normal cells from immune mediated cell death. This interaction is believed to be an inhibitory pathway that helps to prevent overstimulation of immune responses and contributes to the maintenance of immune tolerance to self-antigens.

Aberrant expression of PD-L1 by tumour cells has been reported in a number of human malignancies, including urothelial, ovarian, breast, cervical, colorectal, pancreatic, gastric cancer, melanoma, glioblastoma, renal and non-small cell lung cancer (NSCLC). Expression of PD-L1 or PD-L2 on tumour cells limits and inhibits the anti-tumour immune response, enabling immune evasion by the tumour cells. Tumour PD-L1 membrane expression can be constitutive through oncogenic processes or induced by activated tumour antigen-specific T cells that produce interferons. Expression of PD-L1 on tumour cells has also been studied as a prognostic biomarker in many different primary tumours, with equivocal results.

5 Drake C et al. (2014). Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer. Nature Reviews. Clinical Oncology, 11(1), 24–37.

Blockade of PD-1, or the ligands, results in disinhibition of native immune responses and may reactivate anti-tumour immunity, by restoring T cell responsiveness as well as the ability to mount a direct T cell immune attack against tumour cells. Several antibodies that inhibit the PD-1 pathway by blocking either PD-1 or PD-L1 are being developed for clinical use in a variety of tumour types. Antibodies that inhibit PD-1 block its binding to both PD-L1 and PD-L2, whereas anti-PD-L1 antibodies only block the PD-1:PD-L1 interaction. Figure 3, below, provides an illustration of how checkpoint inhibitors work.

Figure 3. Checkpoint inhibitors



Source: West H. Immune Checkpoint Inhibitors. JAMA Oncol. 2015:1(1):115

Opdivo (nivolumab) is a fully human monoclonal IgG4 antibody (HuMAb) that that blocks the binding of PD-1 receptor to PD-L1 and PD-L2. Nivolumab entered clinical trials in patients with cancer in late 2007. Evidence of clinical activity in multiple tumour types was noted in the initial dose-escalation study, in which the drug was administered in an intermittent schedule. Phase III studies in melanoma, squamous and non-squamous NSCLC and renal cell carcinoma have since been completed.

Unlike conventional chemotherapy drugs that may result in a decrease in tumour size over weeks, immune checkpoint inhibitors can take several months to have this effect. These drugs can also cause an initial increase in tumour size ('pseudoprogression') due to the large number of activated T cells and other immune system cells that enter the tumour and the associated inflammatory effect. This initial increase in size may be followed by shrinking or eradication of the tumour.

Cytotoxic T lymphocyte-associated PD-1 and PD-L1, PD-L2 interactions are believed to have an important role in maintaining immunologic homeostasis and immune tolerance to self-antigens. The use of checkpoint inhibitors has been associated with a unique spectrum of side effects termed 'immune related adverse events' (irAEs). Management of moderate or severe irAEs requires interruption of the checkpoint inhibitor and the use of immunosuppression (usually corticosteroid). The safety of checkpoint inhibitors in patients with an underlying autoimmune condition is uncertain; there is theoretical concern that therapeutic blockade of these receptors could lead to exacerbations of underlying autoimmune conditions.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 11 January 2016.

At the time of this submission, the sponsor has had two applications to register Opdivo (nivolumab) as a New Biological Entity (NBE) approved by the TGA within a short time frame. These were for the use of nivolumab in the patient populations of advanced melanoma, and squamous and non-squamous non-small cell lung cancer (NSCLC). Each of these applications was approved in early 2016. This submission represents a third application to register nivolumab as a NBE.

On 23 November 2015, the US Food and Drug Administration (FDA) approved Opdivo for the treatment of:

> *'advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy.'*

On 4 April 2016, the European Medicines Agency (EMA) in the European Union (EU) approved Opdivo for the treatment of:

> *'advanced renal cell carcinoma who have received prior therapy in adults.'*

Product Information

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

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type. This application can be seen as an extension of indications. It was submitted as a NBE for administrative purposes prior to the initial decision for the first nivolumab application, to facilitate earlier review of the data. A quality evaluation was conducted in the first nivolumab application and as a result, there was no requirement for a further quality evaluation for this submission.

For the quality findings from the first nivolumab NBE application, please see the nivolumab AusPAR for the melanoma and NSCLC based indications available from the TGA website.[6]

III. Nonclinical findings

For the same reasons as described for quality findings above, a nonclinical evaluation was conducted for the first nivolumab application and as a result, there was no requirement for a further quality evaluation for this submission.

For the nonclinical findings from the first nivolumab NBE application, please see the nivolumab AusPAR for the melanoma and NSCLC based indications available from the TGA website.

6 AusPAR for Opdivo nivolumab Bristol-Myers Squibb Australia Pty Ltd. TGA, Canberra: 23 August 2016. Published online: 7 September 2016

IV. Clinical findings

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

Introduction

Clinical rationale

The sponsor's Clinical Overview includes a section titled 'Product Development Rationale'. This section provides an overview of RCC including epidemiology, a description of molecular targeted therapies that are currently available and a description of advanced RCC after prior systemic therapy as an 'unmet need'.

Tyrosine kinase inhibitors (TKI) are described as first line therapy standard treatments as per the ESMO guidelines, and that everolimus and axitinib are the only 2 targeted therapies with a Category 1 recommendation in the NCCN guidelines for use in RCC after first-line TKI therapy. The evidence basis for these two agents in this setting was presented:

- Everolimus: randomised, double blind, placebo controlled Phase III RECORD-1 study, which included 416 subjects with metastatic RCC who received prior sunitinib, sorafenib, or both.
- Axitinib: randomised, controlled, Phase III AXIS trial, which compared two VEGFR TKIs (axitinib and sorafenib) in a total of 723 subjects with advanced RCC who received prior sunitinib, bevacizumab, temsirolimus, or cytokine therapy.

Results for the RECORD-1 and AXIS studies are summarised in Table 3 below.

Table 3. Summary of results of pivotal studies for everolimus and axitinib

	Everolimus (RECORD-1 Study)	Axitinib (AXIS Study)
EFFICACY		*Subjects who received prior sunitinib*:
Median PFS, months	Overall: 4.9 everolimus vs 1.9 placebo (HR 0.33, P < 0.0001) 2nd-line vs 3rd-line everolimus: 5.4 vs 3.8	4.8 axitinib vs 3.4 sorafenib (HR 0.742, P = 0.0002)
ORR, %	2% everolimus vs 0% placebo	11.3% axitinib vs 7.7% sorafenib; RR 1.477 (95% CI: 0.792, 2.754)
Median OS, months	14.8 everolimus vs 14.4 placebo (HR 0.87, P = 0.162)	15.2 axitinib vs 16.5 sorafenib[a] (HR 0.997, P = 0.4902)
SAFETY		
Adverse Events	The most frequently reported drug-related AEs (≥20% of subjects) with everolimus treatment were stomatitis, rash, and fatigue.	The most frequently reported drug-related AEs (≥30% of subjects) with axitinib treatment were diarrhea, hypertension, fatigue, decreased appetite, and nausea.
High Grade Adverse Events	Grade 3 or 4 drug-related AEs reported in >1% of subjects were stomatitis, fatigue, pneumonitis, and infections, which were each reported in 3% of subjects	The most common Grade ≥3 drug-related AEs (≥10% of subjects) were hypertension (17%), diarrhoea (11%), and fatigue (10%)

[a] Median OS in the overall population was 20.1 months in the axitinib group and 19.2 months in the sorafenib group (HR 0.969, P = 0.3744)

On the basis of the poor responses to currently approved therapies, with median progression free survival (PFS) < 6 months with treatment and no demonstrated significant improvement in overall survival, the sponsor states that '*the prognosis for advanced RCC after prior systemic therapy is poor and there is a clear unmet medical need for treatments that improve clinical outcomes'.*

Everolimus was approved by the TGA for second line therapy of advanced RCC in 2009 with the indication: '*Treatment of patients with advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib'*. Axitinib was approved by the TGA for second line therapy in 2012 with the indication: '*For the treatment of patients with advanced renal cell carcinoma after failure of one prior systemic therapy*'.

A brief summary of the clinical development program of nivolumab in RCC and a summary of the regulatory milestones of nivolumab for all indications was provided:

'*There are 4 completed or ongoing studies of nivolumab monotherapy in RCC in previously treated subjects: MDX1106-03, CA209009, CA209010, and CA209025. The current submission includes safety and efficacy data from completed Study CA209025, which focuses on nivolumab monotherapy (3 mg/kg Q2W) at the recommended dose and schedule in subjects with advanced or metastatic RCC after prior therapy. Additional supportive data is provided from CA209010; subjects in CA209010 received nivolumab doses of 0.3, 2, or 10 mg/kg Q3 weeks rather than at the proposed dose and schedule of 3 mg/kg Q2 weeks. In MDX1106-03 subjects were administered nivolumab monotherapy with 1 or 10 mg/kg Q2W, while in CA209009, subjects received nivolumab doses of 0.3, 2, or 10 mg/kg Q3W.'*

Guidance

Through communication between the TGA and the sponsor it was agreed that:

- The sponsor could progress the submission of a parallel NBE application for nivolumab in RCC based on Study CA 209025.
- This submission would have a format similar sponsor's NBE application to register nivolumab in the treatment of non-squamous NSCLC in that it would include components unique to the proposed additional indication but with cross-referencing to prior submissions and evaluations for other components.
- The sponsor confirmed that the RCC application would have the unique components of:
  - One pivotal study (Study CA209025)
  - One supportive study, a Phase II dose ranging study (Study CA209010)
  - Population pharmacokinetics (PK) report for Study CA209025 with exposure analyses
  - An updated Risk Management Plan (RMP) and updated Australian Specific Annex (ASA)
- The TGA agreed that it was acceptable for the dossier content of the RCC application to include only unique documents required for evaluation of Study CA209025 and that other areas did not need to be included, providing there was clear cross referencing to previously submitted documents in the first NBE submission.

According to the sponsor's cover letter, the TGA also agreed to cross-refer to the evaluations of nivolumab from the other 2 NBE applications and only evaluate Study CA209025 related unique documents for this application as indicated for RCC. The evaluator has confirmed with the TGA Delegate that only data unique to the submission needs to be evaluated, unless the evaluator was concerned by an aspect of the submission that required investigation of materials evaluated earlier.

The Clinical Overview describes CHMP (Committee for Medicinal Products for Human Use) Scientific Advice in relation to Study CA209025, provided in October 2011, as supporting the appropriateness of the study design, including, targeted population, stratification factors, choice of comparator, and endpoints for this study in pre-treated advanced RCC, as

well as the overall development in this population as a basis for registration of this indication.

Contents of the clinical dossier

The unique elements of this submission are:

- Pivotal Study CA209025
- Supportive Study CA209010, including an addendum, patient PK and initial tolerability data
- Population PK study reports with analysis in:
  - subjects with solid tumours including advanced or metastatic clear-cell RCC who have received prior anti-angiogenic therapy
  - exposure-response analysis in subjects with advanced or metastatic clear-cell RCC who have received prior anti-angiogenic therapy
- Integrated Summary of Safety: this includes safety data that has been compared across indications in completed studies that used the intended dose and regimen for nivolumab monotherapy. Data from the RCC study (Study CA209025) was compared to NSCLC studies (Studies CA209057, CA209017, and CA209063) and melanoma studies (Studies CA209037, CA209066, and CA209067 (monotherapy arm only)).
- A Clinical Overview, Summary of Clinical Pharmacology Studies and Summary of Clinical Efficacy for RCC.

Paediatric data

The submission did not include paediatric data.

From the Clinical Evaluation Report (CER) for the first nivolumab NBE submission to the TGA, indicated for the treatment of melanoma: *'The sponsor has a Paediatric Investigation Plan (PIP) 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 second quarter of 2018.'*

Good clinical practice

The Clinical Overview provides the following assurance: *'All studies in the nivolumab RCC development program were conducted in accordance with the principles of GCP as defined by the ICH and were conducted to meet the ethical requirement of European Directive 2001/20/EC. For each study, the protocol, amendments, administrative letters, and subject informed consent form received IRB/IEC approval prior to implementation. Compliance audits were performed as part of implementing quality assurance, and audit certificates are provided as applicable in the individual study reports. The quality of data collected and analysed was monitored according to BMS standard operating procedures.'*

Pharmacokinetics

Studies providing pharmacokinetic data

Only limited new PK data was provided in this submission.

Both Study CA209010 and Study CA209025 had an exploratory objective of '*To characterize the pharmacokinetics (PK) of nivolumab and explore the exposure-response*

relationship'. The results from this component of each study have not been reported separately but were included in the population pharmacokinetic analyses included in the submission.

Two separate Population PK analyses were included in this submission. The first includes data from subjects with solid tumours (melanoma, NSCLC and RCC) to develop a pharmacokinetic model, with this then applied to the data from subjects with advanced or metastatic clear-cell renal cell carcinoma who have received prior anti-angiogenic therapy. The second is an exposure-response analysis in subjects with advanced or metastatic clear-cell renal cell carcinoma who have received prior anti-angiogenic therapy.

A sequence of Population PK analyses has been included in the recent nivolumab submissions. Each Population PK analysis has been updated as more data has become available and/or has been focussed on a specific condition and/or has included combination therapy with ipilimumab. The most recent population PK analysis of nivolumab as monotherapy was dated 18 July 2014 and was evaluated in the CER for the first nivolumab NBE submission.

Evaluator's conclusions on pharmacokinetics

This evaluator notes that the conclusion of the evaluator for the first nivolumab NBE submission with respect to the PK data provided was: *'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 to 4 weeks. The PK data included in the submission are considered to meet the requirements of the relevant EMA guideline adopted by the TGA.[7] Overall the PK data are considered acceptable.'*

The additional PK information provided in this submission consisted of a population PK analysis. This analysis provided results consistent with earlier Population PK analyses, with the additional information that nivolumab PK in patients with advanced RCC is similar to that that in subjects with NSCLC or other tumour types.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 4, below, gives the studies submitted that provided pharmacodynamic data along with subtopics covered.

Table 4. Studies providing pharmacodynamic data

Study Identifier	Subtopics
CA209025	Immunogenicity Biomarker assessment and PD-L1 expression
CA209010	QT prolongation PD-L1 expression Immunogenicity

7 EMA Guideline on the investigation of pharmacokinetics of therapeutic proteins

Study Identifier	Subtopics
CA209009	Immunomodulatory activity (including serum chemokine and cytokine levels, tumour infiltration by lymphocyte subsets) Immunogenicity Receptor occupancy PD-L1 tumour expression

Evaluator's conclusions on pharmacodynamics

Some major questions are raised by the pharmacodynamics information that is available:

1. The postulated mechanism of action does not appear to be confirmed
2. The dosing interval selected for the Phase III studies does not appear to be consistent with the pharmacodynamics of receptor interaction, a key component of the postulated mechanism of action
3. The dose chosen for the Phase III study in advanced RCC may be greater than required. Unnecessarily large dosing and excessively frequent dosing may expose the patient to greater risk of adverse consequences.

Mechanism of action

The sponsor has not confirmed the mechanism of action. It is postulated that nivolumab blocks the interaction between PD-L1 expressed on tumour cells and the PD-1 receptor on activated lymphocytes, with this resulting in immune-mediated destruction of tumour cells.

The human immune system is immensely complicated and not fully understood. Immune-mediated cellular destruction would be expected to be accompanied by the release of a variety of cytokines and by changes in the sub-populations of lymphocytes, for example activated helper T cells (CD4+) may release a variety of interleukins (IL 4, 5, 6, 10, and 13) and, once activated, cytotoxic T cells (CD8+) undergo rapid clonal expansion, with this evident in the peripheral circulation.[8]

The essential steps of the postulated mechanism of action are that:

4. Nivolumab binds to the PD-1 receptor
5. PD-L1 and PD-L2 are expressed on tumour cells
6. Binding of nivolumab to the PD-1 receptor blocks the interaction between PD-L1 and PD-L2 on tumour cells, thereby enabling destruction of the tumour cells by immune cells.

This mechanism of action has been investigated in the clinical trial programme through measurement of receptor occupancy, measurement for changes in cytokine levels, chemokine levels and lymphocyte populations and measurement of PD-L1 expression on tumour cells, with correlation of the latter to clinical efficacy.

8 Nijkamp F and Parnham M (eds.), Principles of Immunopharmacology: 3rd revised and extended edition; Springer Basel AG 2011.

Receptor occupancy

PD-1 receptor occupancy by nivolumab has been shown to be dose independent and to be both prolonged and avid. The time course of receptor occupancy was investigated in Study CA209003. This found that after a single dose of nivolumab, a prolonged mean plateau occupancy of greater than 70% was observed, with this persisting even when serum levels of nivolumab were undetectable and that occupancy *'eventually decayed after 85 days*'. In Study CA209009, receptor occupancy with multiple dosing was found to be around 90% within one hour of dose administration and to remain at this level with all subsequent doses. Receptor occupancy was not dose related and there was no decline prior to the next dose (administered every three weeks).

PK studies have demonstrated a half-life of 12 to 20 days, with this dose dependent. Given the apparently avid binding of nivolumab to the PD-1 receptor, as shown by the prolonged high occupancy, the duration of pharmacodynamic effects can therefore be expected to last much longer than the half-life of nivolumab in the circulation. The dosing interval chosen for nivolumab for the Phase III studies of 14 days appears to have been based on the pharmacokinetic measure and may be considerably more frequent than required. Receptor occupancy would be the major factor in the postulated mechanism of action and the dosing interval would more appropriately be based on the duration of this occupancy than the half-life of free nivolumab in the circulation.

Cytokine levels and lymphocyte populations

Apart from an elevation in the levels of two chemokines (CXCL-9 and CXCL-10) that was described in patients receiving nivolumab for renal cell carcinoma (Study CA209009), no notable changes in either cytokine levels or other markers of immunological activity (for example C-reactive protein, interleukins, TNF-alpha, interferon gamma) have been demonstrated. Small increases in the circulating lymphocyte populations of CD4+ and CD8+ were reported on treatment in one study. The lack of change in cytokine levels is in one sense reassuring as it means that widespread activation of the immune system, resulting in a 'cytokine storm', is not occurring. Some signs of immune system activity should, however, be evident given that these patients have metastatic disease and tumour destruction, hopefully, is occurring in many sites.

PD-L1 expression by tumour cells

Considerable variability has been reported in PD-L1 status across the studies, even when the same assay is used; rates of PD-L1 expression using the 5% cut-off ranged from 12% to 53%. Inconsistent findings were reported for efficacy outcomes in relation to PD-L1 status.

From these investigations of the mechanism of action, PD-1 receptor occupancy by nivolumab on peripheral lymphocytes and small increases in the circulating populations of CD4+ and CD8+ T lymphocytes has been demonstrated. However, no corresponding changes in absolute lymphocyte count or circulating cytokine levels have been demonstrated. PD-L1 expression appears to be variable and not to relate to efficacy. These findings, particularly in relation to PD-L1 expression, are not consistent with the postulated mechanism of action.

Dose dependency and tumour response

There was no apparent dose-response relationship across the evaluated dose ranges in subjects in the rate of objective responses for patients with melanoma or RCC. The objective response rate in RCC patients was 27.8% and 31.3% for patients treated with 1 mg/kg and 10 mg/kg respectively. The objective responses observed were 31.4%, 41.2% and 20.0% of melanoma patients treated at 1, 3 and 10 mg/kg respectively. The dose chosen for the pivotal study in patients with advanced RCC (3 mg/kg) is not consistent with these findings. A dose of 1 mg/kg may have been adequate.

Time course of tumour response

Response to nivolumab in terms of measurable decrease in tumour size may be slow. One study of nivolumab therapy in advanced solid organ tumours (Study CA209003) found that, although measurable tumour response occurred within 8 weeks for 46% of responders, tumour shrinkage occurred between 8 weeks and 24 weeks of treatment in another 45% of responders. In 2 studies in patients with advanced RCC, the dose-ranging Study CA209010 and the pivotal Study CA209025, a range of 6 weeks to 25 months was reported in the time to response (investigator assessed). The median duration of response in these studies was around 20 months in Study CA209010 and 12 months in Study CA209025. Tumour response with conventional chemotherapy is expected within days to weeks. The prolonged time course for tumour response seen with nivolumab is consistent with the slower course of immune cell-mediated tumour cell destruction. With the observed receptor occupancy, both degree and duration, frequent administration of nivolumab is unlikely to change this time course.

Exposure response analysis

An exposure-response analysis for efficacy (risk of death and overall survival (OS)) and safety (adverse event leading to discontinuation or death (AE-DC/D)) was provided. These analyses included data from patients with advanced clear cell RCC who had received prior anti-angiogenic therapy in Studies CA209025 (efficacy and safety) and CA209010 (efficacy only). No relationship between exposure (as indicated by average steady state concentration) and overall survival or the occurrence of AE-DC/D was found.

The exposure response analysis for overall survival suggests that male sex, region (Western Europe), favourable baseline Memorial Sloan Kettering Cancer Center (MSKCC) risk score, baseline Karnofsky performance status (KPS), and baseline weight, were significant predictors of OS in subjects with advanced RCC. The risk of death increased with increasing weight. The number of prior anti-angiogenic therapies, age, and PD-L1 status (≥ 1) were not significant predictors of OS. The exposure-response analysis for safety found that, although the risk of AE-DC/D increased with increasing age and baseline body weight, these effects were small and not expected to be clinically relevant

Secondary pharmacodynamics effects

Secondary pharmacodynamics effects have been assessed through a QT prolongation study and investigations of immunogenicity.

QT prolongation

The QT prolongation component of Study CA209010 found that nivolumab was unlikely to cause any clinically meaningful QT prolongation.

Immunogenicity

Anti-drug antibodies (ADA) were investigated in a number of studies in the nivolumab clinical trial programme. The assay used to measure ADA has been through several generations of development, with each assay having different levels of sensitivity. Considerable variability in measured rates of ADA positive patients is notable across the clinical studies, even when the same assay method is used in the studies being compared. The evaluator is not convinced that a reliable assay for anti-nivolumab antibodies has yet been developed and recommends against drawing any conclusions from the measured ADA rates, including the apparent lack of effect on safety and efficacy and the apparent lack of any relationship between infusion related reactions and ADA status.

Dosage selection for the pivotal studies

The study protocol for Study CA209025 provides the rationale for the study design, choice of comparator and nivolumab dosing regimen. Please refer to Attachment 2 for further information.

Efficacy

Studies providing efficacy data

The following studies provided evaluable efficacy data for the use of nivolumab in patients with advanced RCC:

- One pivotal study: Study CA209025
- 3 dose-ranging studies: Studies CA209003, CA209009 and CA209010

Evaluator's conclusions on efficacy

In the pivotal Study CA209025, nivolumab has demonstrated improved OS compared to the mTOR inhibitor everolimus in patients with advanced clear cell RCC who have received one or two previous regimens of anti-angiogenic therapy. The difference was clinically meaningful with overall survival of 55.4% and median survival (Kaplan-Meier estimate) of 25.0 months in the nivolumab arm compared to overall survival of 47.7% and estimated median survival of 19.6 months in the everolimus arm. According to the results for one of the Quality of life (QOL) tools used, nivolumab was not associated with a worse quality of life compared to patients receiving everolimus. However, the results for all QOL measures were not provided. Biological activity in patients with advanced clear cell renal cell carcinoma who have received one or two previous regimens of antiangiogenic therapy was also demonstrated in the dose ranging Studies CA209003, CA209009 and CA209010. These studies did not demonstrate dose dependent response across the range 2 mg/kg to 10 mg/kg and the dosing interval of 2 weeks or 3 weeks.

Study CA209025

The pivotal study for this submission is Study CA209025, a Phase III, open label, randomised multicentre study in which 821 patients with metastatic renal cell carcinoma and a clear-cell component who had previously received one or two antiangiogenic regimens were randomised to nivolumab, with a dosing regimen of 3 mg/kg fortnightly (n = 410), or everolimus, 10 mg orally daily (n = 411). Enrolment in the study was ceased early after independent data monitoring committee review of a pre-planned formal interim OS analysis concluded that the study had met its end point with regard to significant results for overall survival. Crossover from the everolimus arm to the nivolumab arm was allowed following this.

The study was conducted in 146 sites across 24 countries. Enrolment occurred between October 2012 and March 2014. Follow-up for overall survival is ongoing; database lock for the final Clinical Study Report (CSR) provided in the dossier was June 2015. Inclusion criteria were: metastatic RCC as already described; age ≥ 18 years; more than one but nor more than three previous regimens of systemic therapy with these not including an mTOR inhibitor; pre-study archival or recently collected tumour specimens at time of randomisation, disease progression after the last regimen occurring within 6 months prior to study entry, measurable disease according to the RECIST (version 1.1), KPS of at least 70. Patients with central nervous system (CNS) metastases, active autoimmune disease or medical condition requiring systemic immunosuppression or significant organ impairment were excluded. Subjects were randomised 1:1 to nivolumab or everolimus

and stratified according to the following: geographic region (US/Canada versus Western Europe versus Rest of the World), MSKCC risk groups (favourable versus intermediate versus poor), and number of prior anti-angiogenic therapies (1 versus 2). The study was conducted in accordance with Good Clinical Practice (GCP) guidelines and there were no protocol amendments or protocol deviations that would have affected the results of the study.

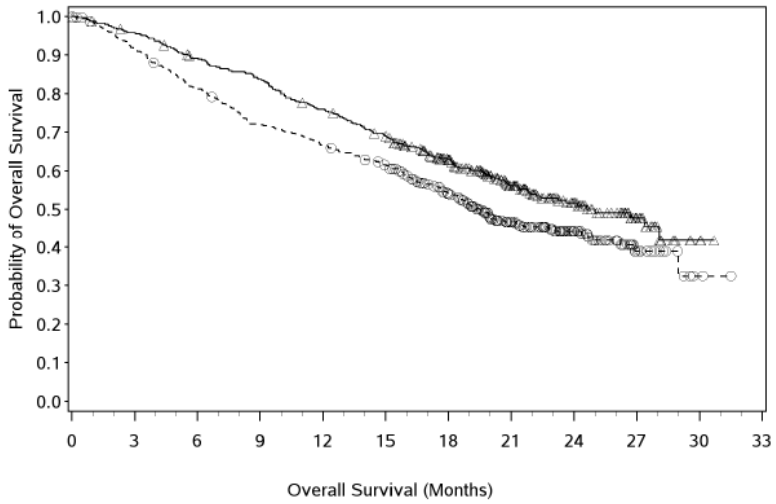
There were 821 patients randomised, of whom 406 in the nivolumab arm were treated and 397 in the everolimus arm. The most common reasons for not receiving treatment in the nivolumab arm included patient no longer meeting study criteria (n = 2) and patient withdrawing consent (n = 8) in the everolimus arm. At the time of analysis, there were 95 patients continuing in treatment (67 in the nivolumab arm and 28 in the everolimus arm). The most common reason for discontinuing treatment in each arm was disease progression (285 patients in the nivolumab arm and 273 patients in the everolimus arm). There were 35 patients in the nivolumab arm who discontinued treatment due to drug toxicity and 53 in the everolimus arm. There were 2 patients in the nivolumab arm and 3 patients in the everolimus arm who discontinued treatment after achieving 'maximum clinical benefit'.

For the randomised patients, the median age 62 years (range: 18 to 88); 88% were White; 75% were male; 83% had 2 or more baseline disease sites; 88% had had prior nephrectomy; 59% and 22% of subjects were in the intermediate or poor Heng risk group at Baseline respectively. These attributes were evenly matched across the treatment arms.

Primary efficacy outcome measure

At the time of the pre-planned interim analysis for the randomised population, with median follow-up for OS of 17 to 18 months, there had been 183/410 (44.6%) deaths in the nivolumab arm compared to 215/411 (52.3%) in the everolimus arm; the hazard ratio (HR) was 0.73 (95% confidence interval (CI) 0.57, 0.93). Median survival (Kaplan-Meier (K-M) estimate) was 25.0 months (95% CI 21.8, not reached (NR)) in the nivolumab arm compared to 19.6 months (95% CI 17.6, 23.1) (see Figure 4, below).

Figure 4. Kaplan-Meier overall survival plot, all randomised subjects



Number of Subjects at Risk

Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

Nivolumab (events: 183/410), median and 95% CI: 25.00 (21.75, N.A.)
Everolimus (events: 215/411), median and 95% CI: 19.55 (17.64, 23.06)
Nivolumab vs Everolimus - hazard ratio and 98.52% CI: 0.73 (0.57, 0.93); p-value: 0.0018

Symbols represent censored observations.
Hazard ratios are estimated using Cox proportional hazard model with treatment group as a sing le covariate, stratified by MSKCC risk group (poor vs. intermediate vs. favorable), the number of prior anti-angiogenic therapies in the advanced/metastatic setting (1 vs. 2) and the region (W. Europe, US/Canada vs. Rest of the World) as entered into the IVRS.
The boundary for statistical significance requires the p-value to be less than 0.0148.

The results of 3 sensitivity analyses (unstratified analysis, analysis using stratification factors as determined at baseline and analysis of all treated subjects) were consistent with the primary OS analysis. The result of analysis of pre-specified subgroups was also consistent, except for the groups 'Asian' and age 75 years or more (absence of demonstrated benefit in the Asian population may be relevant to the target population in Australia).

OS according to tumour PD-L1 expression, positive or negative, appeared to have similar benefit with nivolumab compared to everolimus.

Secondary outcome measures

Secondary efficacy outcome measures included objective response rate (ORR), PFS and duration of response. These outcome measures also favoured nivolumab with 103 patients with best response of CR or PR in the nivolumab arm compared to 22 in the everolimus arm. The objective response rate was 25.1% compared to 5.4% with everolimus (odds ratio (OR) 5.98, 95% CI: 3.68 to 9.72, $p < 0.0001$). The median duration of response was 12 months in all responders, nivolumab and everolimus arms. There was no significant difference in PFS with the K-M estimate for median PFS 4.6 months (95% CI 3.7 to 5.4) in the nivolumab arm and 4.4 months (95% CI 3.7 to 5.5) in the everolimus arm.

These secondary outcome measures were all dependent on assessments of tumour size using the RECIST criteria made by the investigator, with no independent verification of the assessment. Applying RECIST criteria to images of tumour deposits is complex. Detailed 'how-to' descriptions of this were provided in the study protocol but no specific training of investigators was described, nor were any measures of inter-rater reliability. Given that this also was an open label study, there is a strong possibility of both bias and high inter-rater variability. These results should be interpreted with caution.

Consistency of results for the everolimus arm

The results reported for everolimus in this study are consistent with those reported in the pivotal study for TGA approval of everolimus for use in patients with advanced RCC. This was a placebo-controlled trial involving patients whose disease progressed during angiogenesis targeted therapy that reported median progression free survival of 4.9 months (95% CI 4.0 to 5.5) with everolimus 10 mg orally daily compared to 1.9 months (95% CI 1.8 to 1.9) with placebo.[9]

Treatment beyond disease progression

Treatment with nivolumab was allowed to be continued beyond initial RECIST version 1.1 disease progression, at the discretion of the investigator. Of the 179 subjects in the nivolumab group treated in this way, 51 experienced 'non-conventional benefit', with subsequent reduction in tumour size or no further increase in tumour size. No other outcome measures were described for this group. Insufficient information has, therefore, been provided to support continuing treatment beyond disease progression.

Quality of life assessments

QOL at Baseline, during and after treatment was assessed using the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI) Disease-Related Symptoms (DRS) scale. This found similar results for both the nivolumab and everolimus arms at baseline and follow-up visits but a small difference of 2 to 4 points in the 36 point score that favouring nivolumab during treatment. The clinical meaning of this difference is unclear but the results indicate that nivolumab does not worsen quality of life compared to everolimus. Results for the other quality of life measure described in the study protocol (EQ-5D) were not described in the CSR so it is not known whether the results for this measure concur with the results for the FKSI-DRS. Results for Health Resource Utilisation data were also not presented in the CSR.

Other studies

There are three open label dose ranging studies that describe the investigation of nivolumab treatment in patients with advanced clear cell carcinoma who have received prior systemic therapy: Studies CA209003, CA209009 and CA209010. Of these, only Study CA209010 in included in the sponsor's evaluation of efficacy and safety for reasons that are not clear to the evaluator. Study CA209003 included patients with different advanced solid organ tumours: 34 patients had advanced RCC. Studies CA209010 and CA209009 included patients with advanced RCC, although 24 of the patients in Study CA209009 had not received prior therapies. Efficacy results from these studies are roughly similar and consistent with the pivotal study (see Table 5, below). Both the pivotal study and Study CA209010 found a lower median PFS (of around 4 months) compared to Study CA209009.

Table 5. Results from other studies investigating nivolumab in patients with advanced RCC who have received prior therapies

Study identifier	Patient number	Dosing regimen	ORR	Median PFS months	Median OS (months)
CA209003	16	1 mg/kg Q2W	27.8%	NA	NR
	18	10 mg/kg	31.3%		

9 Australian Product Information (PI) for everolimus. Via the TGA website, April 2016.

Study identifier	Patient number	Dosing regimen	ORR	Median PFS months	Median OS (months)
		Q2W			
CA209009	22	0.3 mg/kg Q3W	15% (overall)	11.6	16.4(95% CI 10.1 to NR)
	22	2 mg/kg Q3W		12.4	NR
	23+24*	10 mg/kg Q3W		29.9	25.2 (95% CI 12.0 to NR)
CA209010	59	0.3 mg/kg Q3W	20%	2.7	18.5 (80% CI 16.2 to 24.0)
	54	2 mg/kg Q3W	22%	4	25.5 (80% CI 19.8 to 31.2)
	54	10 mg/kg Q3W	20%	4.2	24.8 (80% CI 15.3 to 26.0)
CA209025	406	3 mg/kg Q2W	25%	4.6	25

NR = Not reached at time of analysis; NA = not available; ORR = Objective response rate; PFS = progression free survival; OS = overall survival; Q2W = every 2 weeks; Q3W every 3 weeks.
*24 patients had not received prior systemic therapies

Selection of dose and dosing interval

Selection of dose and dosing interval for the pivotal study was apparently based on Study CA209003. This dose ranging study included patients with a number of different types of advanced solid organ tumours, including RCC, melanoma and NSCLC. Dose dependency in terms of tumour response was not demonstrated for RCC or melanoma. Some dose-dependency was demonstrated for NSCLC. A dose of 3 mg/kg given fortnightly was, however, chosen as the Phase III dose for all tumour types.

As described above there are three dose ranging studies that describe the investigation of nivolumab treatment in patients with advanced clear cell carcinoma who have received prior systemic therapy with dose levels of 0.3, 1, 2 and 10 mg/kg and dosing intervals of two or three weeks. Efficacy measures in these studies included measures of tumour response as assessed, in general, by the investigator using the RECIST criteria (including ORR, duration of response, PFS with tumour response) and OS. According to the results of these studies (shown in the table above and described below), no particular dose or dosing interval appeared to offer any advantage in these studies.

- In Study CA209010, 168 patients received 0.3 mg/kg or 2 mg/kg or 10 mg/kg every three weeks (50 to 60 patients in each arm). At the time of an updated analysis of OS provided in an addendum to the study, median OS was reached for all three treatment groups and was 18.5 months (80% CI 16.23, 23.98), 25.5 months (80% CI 19.78, 31.24), and 24.8 months (80% CI 15.31, 25.95), for the 0.3, 2, and 10 mg/kg groups, with no significant difference between treatment arms.
- In Study CA209003, 34 patients with RCC received 1 mg/kg or 10 mg/kg every two weeks. This found response rates of 27.8% and 31.3% for subjects treated with 1 and

10 mg/kg nivolumab, respectively and an estimated 1 year OS rate of 70%. The median duration of response was 56 weeks for each dose.

- In Study CA209009, 91 patients received 0.3, 2.0, or 10.0 mg/kg every three weeks. The median OS for each group (95% CI) was 16.4 months (95% CI 10.1, not reached (NR)) for 0.3 mg/kg, NR for 2 mg/kg, 25.2 months (95% CI 12.0, NR) for 10 mg/kg. The estimated 1 year OS rate in this study was 75% (95% CI 64 to 83).

The lack of dose dependency reported in these dose-ranging studies is consistent with the pharmacodynamics studies that demonstrate high PD-1 receptor occupancy, at even low levels of serum nivolumab and small doses of nivolumab, with no dose dependent effect on receptor occupancy rates. In the pharmacodynamics component of Study CA209009, receptor occupancy was reported to be ≥ 90% at all doses (0.3 to 10 mg/kg). These studies also demonstrated avid binding of nivolumab to the PD-1 receptor, with the receptor occupancy plateau rate of 70% persisting for more than 57 days after a single dose of nivolumab.

It is not clear to the evaluator that the dose of 3 mg/kg is necessary for patients with advanced renal cell carcinoma; similar efficacy may have been achieved with a dose of 1 mg/kg given every 2 weeks or 2 mg/kg every three weeks. The dosing interval of two weeks appears to have been based on the half-life of nivolumab and may not have taken into account the prolonged and avid binding to the PD-1 receptor, that is the presumed basis of the therapeutic effect.

Safety

Studies providing safety data

The following studies provided evaluable safety data for the use of nivolumab in patients with advanced RCC:

- One pivotal study: CA209025
- 3 dose ranging studies: CA209003, CA209009 and CA209010

Patient exposure

Table 6, below, details the numbers of patients with advanced RCC exposed to nivolumab

Table 6. Exposure of patients with advanced RCC to nivolumab and comparators in clinical studies.

Study type/ Identifier	Controlled Studies		Uncontrolled Studies
	Nivolumab	Everolimus	
Dose Ranging:			
CA209003			34
CA209010			168
CA209009			91

Study type/ Identifier	Controlled Studies		Uncontrolled Studies
Pivotal:			
CA209025	406	397	

In the pivotal study 406 subjects received at least 1 infusion of nivolumab and 397 subjects received at least one oral dose of 10 mg of everolimus. At the time of the database lock for this CSR (18 June 2015), 708/803 (88.2%) patients had discontinued study therapy: 339 subjects (83.5%) in the nivolumab group and 369 subjects (92.9%) in the everolimus group. The majority of subjects (82.0%) in the nivolumab group received ≥ 90% of the planned dose intensity. In the everolimus group, 68.5% of subjects received ≥ 90% of the planned dose intensity.

The median duration of nivolumab treatment was 5.54 months (95% CI: 5.06, 6.93), with a median of 12 doses received (range 1 to 65). For everolimus treatment, the median duration of treatment was 3.71 months (95% CI: 3.29, 4.14), with a median daily dose of 9.94 mg/day (range 2.1 to 10.0). The mean cumulative dose of nivolumab was 57.72 mg/kg (standard deviation (SD) 49.03); the median cumulative dose was 36.03 mg/kg (range 0.5 to 195.1).

A higher proportion of subjects in the nivolumab group had therapy lasting > 6 months as compared to the everolimus group, which persisted for duration of therapy > 12 months.

Safety issues with the potential for major regulatory impact

Immune mediated adverse reactions

Adverse events (AE) that were consistent with irAEs were considered select AEs in the clinical study programme and included endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, nephritis, and rash. These have been described above according to their occurrence in the studies involving patients with RCC and patients from the registrational studies. These reactions are the main issue so far identified that have the potential for major regulatory impact.

These reactions do not appear to be common in patients receiving nivolumab, although it is not clear how easily they may be distinguished from a non-immune cause for example, in Study CA209025.

For further discussion of immune mediated adverse events (IMAE), see Attachment 2.

Post-marketing data

Two Periodic Safety Update Reports (PSUR) were available at the time of the second round clinical evaluation.

At the time of evaluation, there have been over 8000 patients exposed to nivolumab through the clinical study programme, including patients exposed to nivolumab in combination with another agent such as ipilimumab. No information regarding this total population was provided in the sponsor's Summary of Clinical Safety or the Clinical Overview. According to the draft PI, there have been 1728 patients exposed to nivolumab in completed registrational studies. The patients in the registrational studies can be used to provide an overview of the more common adverse events and to determine if there are differences in these according to tumour types. Pooling of information across the studies can also facilitate in describing the more common immune-mediated adverse reactions.

For detection of the less common immune mediated adverse reactions, the whole population should be used.

Nivolumab has been approved for use in Australia, after prior therapies, in advanced melanoma and NSCLC (squamous and non-squamous) with a dosing regimen of 3 mg/kg every two weeks. Additional safety information is available from the registration studies for these indications.

A full evaluation of safety data from the clinical study program and the pooled registrational studies described above is available in Attachment 2.

Evaluator's conclusions on safety

The evaluator is of the opinion that the safety for the proposed indication has not been adequately characterised by the sponsor. The assessment of safety provided in the sponsor's Summary of Clinical Safety and Clinical Overview is limited to the pivotal Study CA209025 and the dose-ranging Study CA209010. Reference has been made to the safety profile of nivolumab in other solid organ tumour types but only to enable comparison of the safety profile as seen in patients with RCC.

The sponsor has stated that adverse events are not dose related and included the dose-ranging Study CA209010 in their safety assessment. However, two other dose ranging studies that included patients with advanced RCC, Studies CA209009 and CA209003, were not included in the safety assessment. An overview of the frequency of AEs in all patients exposed to nivolumab has not been provided, although such an overview is available in the EMA's Summary of Product Characteristics (SmPC) (for patients with melanoma and NSCLC). An overview of the frequency of AEs in all patients with advanced RCC exposed to nivolumab was also not provided; the overview provided above was constructed by the evaluator from the CSRs of the relevant studies where this information was able to be located (patients with RCC in Study CA209003 could not be included).

Nivolumab has been recognised as a having a unique adverse effect profile due to the occurrence of IMAEs and has been rapidly introduced into clinical practice for a number of indications. The sponsor has stated that the occurrence of IMAEs is not related to tumour type. According to reports in individual studies, the frequency of IMAEs appears to be low but severity seems highly variable. As the number of patients treated in the registrational studies for the different indications is relatively small, dependence on each of these studies individually to satisfactorily describe IMAEs is not possible. A comprehensive overview of the occurrence of IMAEs across all tumour types was not provided in the sponsor's Summary of Safety and Clinical Overview. Some information was available in the proposed PI, although this was limited to registrational studies rather than the whole population exposed to nivolumab monotherapy, and has been included in the evaluator's assessment above. A more detailed depiction of each of the categories of IMAE is needed and this may be best obtained through a cumulative review for each category and type of IMAE, with this including all patients exposed to nivolumab. A better understanding of both the frequency of occurrence and the range of severity (according to clinically important measures such as need for hospitalisation and organ support and including any associated deaths) and the treatments used is essential for the risk-benefit analysis of the use of nivolumab for the proposed indication and any future indications. This information is also essential if appropriate advice for the recognition and management of these conditions is to be is to be provided in the PI and in educational materials provided to the patient and healthcare professionals. The evaluator notes that in regard to 2 of the 5 patients who died due to pneumonitis in Study CA209003, the draft RMP states: '*In the first 2 subjects, there was a delay of approximately 1 to 2 weeks between the onset of symptoms and treatment with high doses of corticosteroids. Earlier recognition and treatment with higher dose corticosteroids may have led to a different outcome, as has been*

reported for GI toxicity elicited by ipilimumab.' The occurrence of severe IMAEs and deaths due to IMAEs may have been under-estimated in the clinical studies due to lack of investigator familiarity with the varying manifestations of these reactions. Similarly, milder manifestations may also have gone un-diagnosed and untreated, for example the high incidence of cough and dyspnoea across the clinical studies is suggestive of un-diagnosed pneumonitis; the high incidence of fatigue is suggestive of endocrinopathies.

The following description of safety is compiled from various sources within the sponsor's dossiers and should not be regarded as complete.

Study CA209025

In Study CA209025, safety was evaluated in 406 patients with advanced clear cell RCC who had previously received at least one anti-angiogenic therapy. The most common (greater than or equal to 20%) adverse reactions included fatigue, cough, nausea, rash, dyspnoea, diarrhoea, constipation, decreased appetite, back pain, and arthralgia. The most common (greater than or equal to 30%) laboratory abnormalities which have worsened compared to baseline included increased creatinine, lymphopenia, anaemia, increased aspartate transaminase, increased alkaline phosphatase, hyponatraemia, elevated triglycerides, and hyperkalaemia.

Serious adverse events (SAE) were reported in 47% of patients. The most common SAEs (greater than or equal to 2%) were acute kidney injury, pleural effusion, pneumonia, diarrhoea and hypercalcaemia. Nineteen deaths were reported within 30 days of the last nivolumab dose. 15 were attributed to progressive disease and 4 due to pneumonia, suicide, heart failure, and myocardial infarction. IMAEs, including pneumonitis, diarrhoea/colitis, hepatitis, nephritis and endocrinopathies were reported. No deaths were attributed to IMAEs.

There was a higher incidence of deaths, SAEs and drug related AEs in the everolimus arm compared to the nivolumab arm.

Studies CA209009, CA209003 and CA209010

Doses ranging from 0.3 mg/kg to 10 mg/kg and dosing interval of 2 weeks or 3 weeks were used in these studies. The adverse event profile seen in these studies was similar to that seen in the pivotal study, with no evidence of dose-dependence except for an increase in infusion-related reactions with the dose 10 mg/kg. Immune mediated adverse reactions were reported in each study, although no deaths were attributed to these in Studies CA209009 and CA209010. There were 5 deaths attributed to immune mediated pneumonitis in Study CA209003, although these occurred in patients with NSCLC (n = 4) and colorectal cancer (n = 1).

Registrational Studies (using dosing regimen of 3 mg/kg every 2 weeks)

This comprised a total of 1728 patients from seven studies. The individual studies and pooled data showed a similar overall adverse event profile to that seen with Study CA209025, with fatigue the most common (> 40%) and nausea, diarrhoea, dyspnoea, constipation and decreased appetite reported in more than 20%. The most common Grade 3 to 4 events were fatigue, dyspnoea and back pain. Immune mediated adverse reactions were reported in each of these studies.

Immune mediated adverse reactions (IMAE)

This group of adverse reactions is the most concerning with regards to safety and appears to be poorly understood and characterised. It is concerning that the sponsor has not used all of the information available to attempt to better understand the manifestations of these reactions or to determine the most effective treatment regimens.

IMAEs have been reported in all studies. The frequency of occurrence in individual studies is difficult to determine as the reported rates are dependent on investigator recognition of the event as immune-mediated for example in Study CA209025:

- Diarrhoea/colitis occurred in 115 (28.3%) subjects in the nivolumab group, with this considered to be an IMAE in 13 (3.2%) patients by the investigator
- Hepatitis occurred in 62 (15.3%) subjects in the nivolumab group, with this considered to be IMAE in 6 (1.5%) patients by the investigator
- Pneumonitis occurred in 26 (6.4%) subjects, with this considered to be an IMAE in 18 (4.4%) patients by the investigator.
- Nephritis and renal dysfunction occurred in 75 (18.5%) subjects, with this considered to be an IMAE in 12 patients by the investigator.

Data regarding select AEs from the registrational studies is provided in the proposed PI, with frequencies as shown in Table 7, below.

Table 7. Overview of IMAEs in the registrational studies (Patient number = 1728)

IMAE category	Number (%) reported	Number treated with systemic immunosuppression	Number discontinuing nivolumab due to IMAE
Pneumonitis	56 (3.2)	41	14
Colitis	235 (13.6)	34	12
Hepatitis	121 (7)	19	15
Nephritis	55 (3.2)	15	2
Skin reaction	484 (28.0)	18	3
Thyroid dysfunction	149 (8.6)	?	?
Hypophysitis	4 (0.23)	?	?
Adrenal insufficiency	10 (0.58)	?	?
Diabetes mellitus	3 (0.17)	?	?
Encephalitis	?	?	?
Guillaine-Barre	< 1%	?	?
Pancreatitis	< 1%	?	?
Uveitis	< 1%	?	?
Autoimmune neuropathy	< 1%	?	?
Myasthaenic syndrome	< 1%	?	?

In general, these reactions appear to be mild (Grade 1 or 2) although more severe reactions, including fatalities have been reported. The following deaths have been attributed to immune mediated adverse reactions in patients receiving nivolumab:

- 5 due to study drug related pneumonitis reported in Study CA209003
- 1 due to pneumonitis in a patient also receiving ipilimumab in Study CA209069
- 1 due to entero-colitis and pancreatitis in a patient also receiving ipilimumab in Study CA209004
- 1 due to encephalitis in Study CA209057
- 1 due to pneumonitis in Study CA209063

From the narratives in Studies CA209010, CA209025 and CA209009 that have been read by the evaluator it is possible that this under-represents the number of patients whose deaths may be related to immune mediated adverse reactions. This can reflect the clinical difficulty of determining the cause of illness and death in complex patients for example, if a patient dies from sepsis due to immunosuppression required to treat an immune mediated adverse reaction, this death may or may not be attributed to the study drug by an investigator; deaths due to systemic inflammatory response syndrome (SIRS) multiple organ dysfunction syndrome (MODS) or multiple organ failure (MOF) may have been attributed to sepsis or cardiac failure or 'other' instead of to immune mediated AEs; unexpected deaths at home may be due to a cardiac arrhythmia and myocarditis; deaths from respiratory failure may be attributed to pneumonia rather than pneumonitis. It may also reflect a lack of familiarity of the investigators with immune mediated adverse reactions, resulting in a failure to either consider or diagnose these reactions. Similarly, less severe manifestations of IMAE may not have been recognised by the investigators.

A lack of familiarity with immune mediated adverse reactions associated with nivolumab treatment in the greater population of healthcare professionals who may become involved in the care of these patients is extremely concerning and represents a major safety risk. From the narratives provided, IMAE may take a fulminant course and require prompt recognition and early institution of systemic immunosuppressive therapies. This has been demonstrated in Study CA209003 in 2 of the 5 patients who died due to pneumonitis in this study: according to the draft RMP: '*In the first 2 subjects, there was a delay of approximately 1 to 2 weeks between the onset of symptoms and treatment with high doses of corticosteroids. Earlier recognition and treatment with higher dose corticosteroids may have led to a different outcome, as has been reported for GI toxicity elicited by ipilimumab*.' Patients who become acutely unwell may present to their local doctor or local emergency department for emergency care. Delays in appropriate care and a worse outcome may result from lack of awareness of the unique side effect profile of checkpoint inhibitors. The EMA has sought to address this lack of familiarity through the use of a patient alert card (including advice for both patient and medical practitioners providing emergency care) and physician education packages. The evaluator strongly recommends that the TGA also adopt this approach

In conclusion, this assessment of safety is considered incomplete by the evaluator and will need to be revised and completed following the evaluation of the sponsor's responses to the Clinical Questions. On the information currently available, additional safety measures that target the patient and healthcare professionals' awareness of IMAE are strongly recommended as the use of nivolumab becomes more wide spread.

First Round Benefit-Risk Assessment

First round assessment of benefits

Nivolumab has demonstrated clinically meaningful improved overall survival in comparison to everolimus in patients with advanced clear cell RCC who have progressed despite prior anti-angiogenic therapy. At the median follow-up of 17 to 18 months, there had been 183/410 (44.6%) deaths in the nivolumab arm compared to 215/411 (52.3%) in the everolimus arm; HR 0.73 (95% CI 0.57, 0.93). Median survival (KM estimate) was 25.0 months (95% CI 21.8, NR) in the nivolumab arm compared to 19.6 months (95% CI 17.6, 23.1).

Despite the small improvement in overall survival with nivolumab, outcome overall was very poor. At the time of analysis for the primary outcome measure (median follow-up of 17 to 18 months), only 67/410 patients in the nivolumab arm and 28/411 patients in the everolimus arm were continuing with study treatment. A total of 398/821 (48.5%) of patients had died and only 72/821 (8.8%) patients had not developed disease progression.

For the increase in overall survival and estimated 5 months increase in median duration of survival to be meaningful to patients, it is important that it be associated with an acceptable quality of life. The study protocol for the pivotal study describes the use of 2 QOL tools, the FKSI-DRS and the EQ-5D, together with the collection of health resource utilisation data. The results using the FKSI-DRS tool were presented in the CSR. This found no difference in median scores between the two arms at Baseline and at the follow-up visit. There was a small difference favouring nivolumab in the median scores during treatment. The results of the EQ-5D and health resource utilisation were not presented in the CSR nor is there any explanation given for their omission.

Everolimus and axitinib are currently approved as second line agents for the treatment of advanced RCC. On the basis of improved survival and no worsening in QOL, as demonstrated in Study CA209025, nivolumab appears to offer an advantage over everolimus. No information has been presented to indicate if nivolumab offers any advantage over axitinib.

The wording of the proposed indication is also concerning. The sponsor proposes the indication of monotherapy in '*patients with advanced renal cell carcinoma (RCC) after prior therapy'* without any definition of prior therapy or distinguishing the type of RCC. This is not consistent with the population studied in the pivotal trial in which patients with RCC with a clear cell component were included if they had received prior anti-angiogenic treatment. In the discussion of the selection of comparator for the pivotal study, the sponsor noted that '*A population of subjects who received prior anti-angiogenic therapy, rather than subjects who have received any prior systemic therapy, was chosen because the type of prior regimen received has been shown to have an impact on clinical outcome in subjects with pre-treated advanced or metastatic RCC*'. The wording 'prior therapy' may refer to surgery alone or to systemic therapies other than anti-angiogenic therapy. The indication, as proposed, could result in patients receiving nivolumab in whom the efficacy and safety has not been established for example, patients with non-clear cell carcinoma or patients who have not received anti-angiogenic therapy. The wording of the indication, therefore, should be more specific if the benefit for nivolumab is to be realised. The evaluator notes that the indication approved by the FDA used the wording: *'patients with advanced RCC who had received prior anti-angiogenic therapy'*. Wording that most accurately reflects the population in the pivotal study (in whom efficacy was demonstrated) is *'patients with advanced clear cell RCC who had received prior anti-angiogenic therapy'.*

First round assessment of risks

In general, the safety of nivolumab appears to be acceptable in a population of patients with advanced RCC with poor prognosis. However, the evaluator is concerned that a full picture of the most concerning risk, immune-mediated adverse reactions, has not been provided. As a result, the frequency and possible clinical consequences of these reactions cannot be adequately assessed. Reliance on post-marketing measures to enable better characterisation of these reactions appears inappropriate given that there is considerable information that should be available from the clinical study programme.

As an example of the evolving nature of the safety of nivolumab and the need for regular comprehensive review of safety, with this included in any submissions for new indications, the evaluator notes the following in the proposed RMP:

'Newly identified safety concerns since the last EU-RMP submitted:

Across the ongoing clinical program, a new adverse drug reaction (ADR) of toxic epidermal necrolysis (TEN) was identified based on one additional case of TEN with fatal outcome on nivolumab monotherapy (2 previous cases included one case that occurred on subsequent Bactrim after discontinuation from nivolumab and ipilimumab (one dose) due to colitis, and 1 case occurred on subsequent ipilimumab after discontinuation from nivolumab due to erythema multiforme). The estimated frequency of TEN is rare (3 cases (0.03%, 3/8490)) and TEN is added to the immune-related rash category under important identified risks.

Another new ADR of encephalitis was identified during routine pharmacovigilance signal detection activities from the ongoing nivolumab clinical program. As of 29 April 2015, five cases (1 on nivoliumab monotherapy, 4 on combinational therapies of nivolumab + ipilimumab) were identified and considered related to study drug(s). The estimated frequency of encephalitis was rare at 0.01% (1/6718) in nivolumab monotherapy and uncommon at 0.2% (4/1772) in nivolumab + ipilimumab combination therapy studies. Based on this information, encephalitis was considered as an ADR of nivolumab and is added to the 'other immune-related adverse reactions' category under important identified risks.'

Encephalitis is mentioned under 'Other Immune-related adverse reactions', without fatal outcome being described, in the proposed PI. Toxic epidermal necrolysis (TEN) is not explicitly mentioned in the proposed PI. The term *'Immune-related rash and severe skin reactions'* which is used has quite different clinical connotations from TEN. Neither of these irARs was reported in Study CA209025 or Study CA209010. Reliance on the safety assessment as provided by the sponsor in the Summary of Clinical Safety and Clinical Overview would result in under-appreciation of the potential significance of IMAE.

The evaluator is also concerned that there has not been sufficient consideration given to where and how these patients may present for emergency care. Patients from outer suburban, rural and regional centres in Australia may receive their treatment with nivolumab in tertiary referral hospitals in the nearest city but may present to their local doctor or local emergency department when they become acutely unwell. Given that nivolumab is new in clinical practice and has an adverse effect profile unlike that of any other class of anti-tumour treatment, medical practitioners providing emergency care cannot be expected to be familiar with immune mediated adverse reactions. As a result, appropriate treatment may be delayed, with worse outcomes for the patient. Early treatment of the severe manifestations of immune mediated adverse reactions is essential. The evaluator notes that in regard to 2 of the 5 patients who died due to pneumonitis in Study CA209003, the draft RMP states: '*In the first 2 subjects, there was a delay of approximately 1 to 2 weeks between the onset of symptoms and treatment with high doses of corticosteroids. Earlier recognition and treatment with higher dose corticosteroids may have led to a different outcome, as has been reported for GI toxicity elicited by ipilimumab*.'

The evaluator notes that similar concerns have been addressed by other regulatory bodies, in particular the EMA. A requirement for marketing both PD-1 monoclonal antibodies (pembrolizumab and nivolumab) in the EU is that the patient is provided with a patient alert card and that physician education be provided.

The evaluator is of the opinion that, if nivolumab is to be approved for the proposed indication, this approval should be contingent upon the adoption of additional safety measures as indicated by the changes in product documentation recommended. These include:

1. Substantial revision of the product information

The proposed version constitutes a safety risk due to excessive length impairing easy access to important safety information:

2. Revision of the Consumer Medicine Information (CMI)
3. Introduction of a patient safety alert in wallet card format
4. Introduction of a Healthcare professional (HCP) education brochure

The evaluator notes that the ASA of the RMP describes 'additional risk minimisation measures' of a Patient Communication tool and HCP tool. The evaluator has been able to locate a limited description of an 'Adverse Reaction Management Guide' and 'Patient Alert Card' in the RMP. It is not clear to the evaluator as to whether these are the same as the 'Patient communication tool' and 'HCP tool' and no mock-ups or samples are provided in the draft RMP. Nor is it clear to whether these additional risk management measures have, in fact, been implemented in Australia.

Serious consideration should also be given to a sponsor-funded registry of Australian patients receiving nivolumab to facilitate post-marketing monitoring of use and safety. Participation in the registry could be used to identify health services to target with educational resources.

First round assessment of benefit-risk balance

The evaluator recognises that the proposed population is a group with poor prognosis and that the risks with treatment may be less of a concern in such a group if there is a meaningful increase in overall survival. However, it is important to ensure that these patients are not just living longer but also living better. The treatment regimen should not be so onerous and the side effects of treatment so unpleasant that their additional months of life are too miserable for them to benefit from this time. Given the unique profile of adverse events, it is also important that measures are taken to ensure early and appropriate treatment is provided for these. A careful evaluation of the risks and benefits of treatment, together with how the risks may be minimised, is therefore, essential.

Due to the number of clinical questions that address many aspects of the use of nivolumab for the proposed indication, the evaluator is unable to make an adequate assessment of benefit-risk balance. This is largely due to:

- Lack of confirmation of the postulated mechanism of action
- Incomplete characterisation of immunogenicity
- Missing quality of life and health resource utilisation results from the pivotal study
- Incomplete characterisation of the safety of nivolumab, particularly in relation to immune-mediated adverse reactions
- Lack of risk minimisation strategies to address the predictable deficiencies in familiarity with immune-mediated adverse reactions in medical practitioners who may be required to provide emergency care.

First Round Recommendation Regarding Authorisation

The evaluator is unable to make a recommendation regarding authorisation at this time. Any recommendation to be made by the evaluator will be dependent on the responses provided by the sponsor to the Clinical questions (see Attachment 2) posed by the evaluator. Consideration will also need to be given by the evaluator to the sponsor's response to the proposed additional documentation (patient safety information wallet card and health professionals' education brochure) and revision of the proposed product information and consumer medicines information.

Clinical Questions and Second Round Evaluation of clinical data submitted in response to questions

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

Second Round Benefit-Risk Assessment

Second round assessment of benefits

Table 8 (below) summarises the second round assessment of benefits along with strengths and uncertainties of those benefits.

Table 8. Second round assessments of benefits, strengths and uncertainties

Benefits	Strengths and Uncertainties
Study CA209025 demonstrated clinically meaningful improvement in overall survival in patients with advanced clear cell RCC who have received prior anti-angiogenesis therapy in comparison to everolimus. The median of OS for nivolumab group was 25 months, whereas subjects treated with everolimus achieved a median of OS of 19.55 months (HR: 0.73 (98.52% CI: 0.57, 0.93); stratified log-rank test p value = 0.0018).	Sensitivity analyses were consistent. Secondary endpoint of ORR was consistent. Secondary endpoint of PFS was not consistent; it showed no difference between the two arms of the study with PFS of 4.6 months in the nivolumab arm and 4.4 months in the everolimus arm. Improvement in OS was independent of PD-L1 status.
Study CA209025 found that QoL in comparison to baseline was not worsened by treatment with nivolumab and was improved in comparison to everolimus.	Analysis was reported during the treatment period only.
Study CA209025 found that health resource utilisation was not increased by treatment with nivolumab in comparison to everolimus.	Data regarding non-protocol medical visits and hospital admissions were collected. Analysis was provided for Weeks 4 to 16 only.
Studies CA209010, 209009, and 209003 reported ORRs in patients with advanced RCC that were consistent with	ORR was dependent on investigator assessed tumour response; all studies were open label.

Benefits	Strengths and Uncertainties
Study CA209025.	
Only patients with clear cell RCC were included in the pivotal study and other dose escalation studies.	There is no clinical data to guide use in patients with non-clear cell RCC.
Only patients with prior anti-angiogenesis therapy were included in the pivotal study.	There is minimal clinical data to guide use in patients with RCC who have not received prior anti-angiogenesis therapy.

Both everolimus and axitinib are currently approved as second line agents for the treatment of advanced renal cell carcinoma. On the basis of improved survival and no worsening in quality of life, as demonstrated in Study CA209025, nivolumab appears to offer an advantage over everolimus. No information has been presented to indicate if nivolumab offers any advantage over axitinib.

Second round assessment of risks

Table 9 (below) summarises the second round assessment of risks along with strengths and uncertainties of those benefits.

Table 9. Second round assessment of risks, strengths and uncertainties

Risks	Strengths and Uncertainties
In Study CA209025, rates of adverse events were similar in both arms: Grade 3 or 4 AEs were reported in 53.2% of subjects in the nivolumab group and 56.4% of subjects in the everolimus group; any-grade SAEs were reported in 47.8% of subjects in the nivolumab group and 43.6% of subjects in the everolimus group.	
In Study CA209025, there were no deaths reported that were assessed as related to study drug toxicity.	Deaths due to irAR with nivolumab monotherapy have been reported in other studies. Lack of familiarity on the part of investigators may have resulted in under-recognition of deaths due to irARs in Study CA209025.
In Study CA209025, AEs that were potentially immune mediated occurred commonly: diarrhoea/colitis in 28.3%, hepatitis in 15.3%, nephritis in 18.5% and pneumonitis in 6.4%, although only a small proportion were considered related to study drug therapy by the investigators.	irAR have non-specific presentations with no confirmatory diagnostic test with recognition is dependent on clinical suspicion and familiarity. Lack of familiarity on the part of investigators may have resulted in under-recognition of irARs in Study CA209025

Risks	Strengths and Uncertainties
There were no new safety concerns identified in Study CA209025.	Two patients died from MOF and one patient developed SIRS in Study CA209025 and 209010. Apart from these patients, there may be as many as 51 patients who have been reported as developing SIRS/MODS/MOF during nivolumab treatment. During prospective monitoring specifically for SIRS in a group of 32 patients receiving nivolumab for NSCLC, 12 patients were reported to develop SIRS.
Major safety concerns have been identified with the use of nivolumab monotherapy in other studies in the clinical development programme and with the number of patients exposed increasing. These include fatal and/or serious irARs such as pneumonitis, hepatitis, nephritis, colitis, SJS/TEN, encephalitis, myasthenic syndrome, demyelination, myasthenia gravis, Guillain-Barre syndrome, rhabdomyolysis, myocarditis, myositis, severe infusion reactions, adrenal failure, hypopituitarism, pancreatitis, duodenitis, and gastritis. It is likely that immune related reactions related to every body part will be recognised as patient exposure increases.	irAR have non-specific presentations with no confirmatory diagnostic test, creating diagnostic uncertainty. Recognition is dependent on clinical suspicion. Appropriate education of healthcare professionals involved in the care of patients being treated with nivolumab is essential.
Limitations to information available to prescribers and due to full PI not included as package insert and distribution dependent on internet access.	The PI is an important educational tool. It should be easily accessed both as hard copy and electronically by all prescribers.
Limitations to information available to medical practitioners providing ongoing care to patients with severe irARs.	The evaluator is of the opinion that the HCP tool provides only limited and over-simplified information regarding the ongoing management of irARs. The level of detail provided in the Investigators Brochure is more appropriate.
Limitations to 'Patient Alert Card' with current format 4 pages long.	The intention of a 'Patient Alert Card' is that it be carried at all times by the patient and provides essential basic information, including immediate actions if life-threatening condition, and indicates contacts whereby further information can be obtained. The

Risks	Strengths and Uncertainties
	evaluator does not consider the 4 page format of the current nivolumab card to be suitable for the intended purpose.

Second round assessment of benefit-risk balance

The benefit-risk balance of nivolumab for the indication of: *'Adult patients with advanced RCC (clear cell) who had received prior anti-angiogenic therapy'* is favourable.

Ongoing refinement of the educational/awareness tools of the PI, Patient Alert Card and Healthcare Professionals guide are essential to minimise the risks associated with irARs. A multicentre national observational registry would provide information regarding the safety and efficacy of nivolumab outside of clinical trials in the Australian context.

Second round recommendation regarding authorisation

The evaluator recommends that nivolumab be approved for the indication of:

> *'Adult patients with advanced RCC (clear cell) who had received prior anti-angiogenic therapy'*

Ongoing refinement of the educational/awareness tools of the PI, Patient Alert Card and HCP guide are essential to minimise the risks associated with irARs. A multicentre national observational registry would provide information regarding the safety and efficacy of nivolumab outside of clinical trials in the Australian context.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP): EU-RMP version 4 dated 23 September 2015, data lock point 18 June 2015; and an Australian Specific Annex (ASA) version 3 dated 5 November 2015 which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown below in Table 10.

Table 10. Summary of ongoing safety concerns

Important identified risks	Immune related pneumonitis Immune related colitis Immune related hepatitis Immune related nephritis or renal dysfunction Immune related endocrinopathies Immune related rash (and severe skin reactions)* Other immune related adverse reactions Severe infusion reactions
Important potential risks	Embryofetal toxicity Immunogenicity Cardiac arrhythmias (previously treated melanoma indication only)
Missing information	Paediatric patients < 18 years of age Patients with severe hepatic and/or renal impairment Patients with autoimmune disease Patients already receiving systemic immunosuppressants before starting nivolumab

*Severe skin reactions have been added for Australia per previous TGA request.

Pharmacovigilance plan

Additional pharmacovigilance activities have been proposed for the important identified risks, as well as the important potential risk of cardiac arrhythmia (see Table 11, below). The sponsor has advised that no tumour/indication specific changes have been proposed to the 'Pharmacovigilance' section of the ASA since the TGA approved nivolumab ASA version 2.2 (that is, versions 2.2 through 5).

Table 11. Ongoing and proposed additional pharmacovigilance activities

Safety Concern	Additional activity	Proposed actions/outcomes	Planned submission date
Ongoing studies (EU-RMP)			
Immunogenicity Cardiac arrhythmias (previously treated melanoma indication, only)	Study CA209172: *'A Phase II, single arm, open label, Multicenter Clinical Trial with Nivolumab for Subjects with Histologically Confirmed Stage III (unresectable) or Stage IV Melanoma*	To further characterise immunogenicity and its impact on efficacy and safety To evaluate and characterise	4Q 2017

Safety Concern	Additional activity	Proposed actions/outcomes	Planned submission date
	Progressing Post Prior Treatment Containing an Anti-CTLA-4 Monoclonal Antibody'.	cardiac arrhythmia risk	
	Study CA209171: *'A Single-Arm, Open-Label, Multicenter Clinical Trial with Nivolumab Monotherapy in Subjects with Advanced or Metastatic SQ NSCLC who Have Received at Least Two Prior Systemic Regimens for the Treatment of Stage IIIb/IV SQ NSCLC'.*		4Q 2017
	Study CA209357: '*A US Multisite Observational Study in Patients with Unresectable and Metastatic Melanoma (observational registry)*'[1]		To be determined
Ongoing studies (ASA)			
Immune related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies rash and other irARs (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, and encephalitis) and infusion reactions.	*'Clinical Trial of Nivolumab Combined with Ipilimumab Followed by Nivolumab Monotherapy as First-Line Therapy of Subjects with Histologically Confirmed Stage III (Unresectable) or Stage IV Melanoma'.* At TGA request, this study is included as an Australian-specific additional PV activity (Study CA209401).	To characterise high-grade treatment-related AEs. Global study and Australia is a participant.	Not indicated
Planned Studies (EU-RMP)			
Immune related pneumonitis, colitis, hepatitis, nephritis and	Post-marketing pharmacoepidemiology study: *'Pattern of Use and Safety/Effectiveness of*	To assess use pattern, effectiveness, and safety of	Interim annual reports; Final CSR:

Safety Concern	Additional activity	Proposed actions/outcomes	Planned submission date
renal dysfunction, endocrinopathies rash and other irARs (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, and encephalitis) and infusion reactions.	*Nivolumab in Routine Oncology Practice. Includes patients with melanoma and NSCLC'.* (Study CA209234)	nivolumab, and management of important identified risks of nivolumab. Includes Australian patients	4Q 2024

1) These studies are conditions of the Marketing Authorisation in the EU

Table 12. Ongoing and proposed studies

Study ID	Study description/aim	Final CSR submission
CA209067	Final clinical study report for Study CA209067: '*A Phase III, randomised, double-blind study of overall survival in subjects treated with nivolumab monotherapy, ipilimumab monotherapy, and nivolumab combined with ipilimumab'.*	31 March 2017
To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (for example other genomic-based methods/assays, and associated cut-offs, that might prove more sensitive and specific in predicting response to treatment based on PDL1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, expression of components of antigen-presentation complexes and/or other inhibitory checkpoint receptors/ligands within tumour, and so on) as predictive of nivolumab and/or nivolumab plus ipilimumab combination therapy efficacy. This will be provided for all the approved indications:		
CA209038 and CA209066	Melanoma monotherapy studies	30 September 2017
CA209038, CA209067 and CA20906*	Melanoma combination (with ipilimumab) studies	31 March 2019
CA209017, CA209057 and CA209026	NSCLC studies	31 March 2018
CA209025	RCC studies	31 March

Study ID	Study description/aim	Final CSR submission
and CA209009		2018
CA209009, CA209038 and CA209064.	To further investigate the relation between PD-L1 and PDL2 expression in Phase I studies	31 March 2017
CA209066, CA209057, and CA209025.	To further investigate the associative analyses between PD-L1 and PD-L2 expression conducted in Studies CA209066, CA209057, and CA209025.	30 June 2018
CA209009, CA209038 and CA209064.	To further investigate the possible change in PD-L1 status of the tumour during treatment and/or tumour progression in studies CA209009, CA209038 and CA209064.	30 September 2017

Risk minimisation activities

HCP and patient communication tools were included as additional risk minimisation activities for the important identified risks: Immune related Pneumonitis, Immune related Colitis, Immune related Hepatitis, Immune related Nephritis and Renal Dysfunction, Immune related Endocrinopathies, Immune related Rash, and Other Immune related ARs. This approach has previously been agreed upon with the TGA. The additional risk minimisation activities are:

1. A HCP communication tool (Immune Related Adverse Reaction Management Guide)
2. A patient communication tool in the form of a Patient Alert Card.

Both are intended to facilitate safe and effective use of nivolumab, and both are now available in Australia for the two currently registered indications: metastatic melanoma and squamous and non-squamous NSCLC.

The sponsor has indicated their intention to update the existing educational materials to include the approved RCC indication and updated pooled monotherapy irAR data (pooled monotherapy safety data updated to include data from Study CA209025). In addition, these updates will be aligned to the approved Opdivo PI for the RCC indication as part of this application.

Reconciliation of issues outlined in the RMP report

Table 13 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and the RMP evaluator's evaluation of the sponsor's responses.

Table 13. Reconciliation of issues outlined in the RMP report

Recommendation 1: Safety considerations may be raised by the nonclinical and clinical evaluators through TGA requests for more information and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations raised, the sponsor should provide the necessary information to address

the issue in the RMP.
Sponsor's response: The sponsor confirmed that there have been no requests within the Clinical Evaluation Report to update the RMP to reflect the proposed indication of RCC.
RMP Evaluator comment: The sponsor has addressed the evaluator's RMP questions.
Recommendation 2: The caption for Table 23 in the PI includes reference to 'Section 4.4'. This appears to be a reference to the relevant section of the EU SmPC which is not applicable in Australia. Such references should be removed.
Sponsor's response: The sponsor states this has now been changed in current versions of the PI (The RMP evaluator reviewed a previous version (0.9) 12 November 2015).
RMP Evaluator comment: The draft PI (version 3.3) submitted with the sponsor's response now refers to 'Precautions' rather than 'Section 4.4'.
Recommendation 3: The 'Dosage and Administration' section contains monotherapy dosage instructions for melanoma and NSCLC but not specifically Renal Cell Carcinoma (RCC). From a risk minimisation perspective the dosage and administration advice for the RCC indication should be specifically described.
Sponsor's response: The draft PI version 3.3 includes dosage and administration advice for the RCC indication. (The RMP evaluator reviewed version 0.9, 12 November 2015).
RMP Evaluator comment: The draft PI (version 3.3), dosage for Opdivo monotherapy, now includes renal cell carcinoma.
Recommendation 4: Changes made to the ASA as a result of previous evaluations are relevant to ASA version 3 but have not yet have been incorporated likely due to the timing of the previous applications. A revised ASA, incorporating all previously accepted changes and any relevant new information should be submitted with the responses to TGA questions.
Sponsor's response: Changes made to the ASA as a result of the initial TGA evaluation for the first nivolumab application were not included in Nivolumab ASA version 3 due to timing of the dossier submission for a further application in December 2015. Nivolumab ASA version 2.2 was approved by the TGA as part of the initial Opdivo marketing authorisation application (MAA) on 7 January 2016. Previously agreed changes in Nivolumab ASA version 2.2 have been incorporated into Nivolumab ASA version 4 and ASA version 5.
RMP Evaluator comment: ASA versions 4 and 5 have been updated and include changes made in version 2.2 including: Study CA209-401, an additional pharmacovigilance activity for Australia; and the safety concern 'Immune-related rash' has been renamed 'Immune related rash and severe skin reactions' for Australia as per TGA request.
Recommendation 5: The pharmacovigilance section of the ASA was substantially revised in response to previous TGA evaluation. However these changes have not been included in version 3. A revised ASA, incorporating all previously accepted changes should be submitted with the sponsor's response to TGA questions.
Sponsor's response: As above in TGA recommendation 4.

RMP Evaluator comment: A revised ASA has been submitted, the latest version submitted is number 5.
Recommendation 6: The sponsor should confirm whether there are specific additional pharmacovigilance activities proposed for the RCC indication. If so, details should be included in the RMP documentation.
Sponsor's response: Although the Nivolumab EU-RMP has been updated with data for the new indications, there have been no changes to the nivolumab safety profile since the TGA approved Nivolumab EU-RMP version 3 (that is, versions 3 through version 6). Additionally, no tumour/indication specific changes have been proposed to the Pharmacovigilance section of the ASA since the TGA approved Nivolumab ASA version 2.2 (that is versions 2.2 through 5).
RMP Evaluator comment: The RMP evaluator notes there are no indication specific pharmacovigilance activities planned.
Recommendation 7: The risk minimisation section of the ASA was substantially revised in response to the previous TGA evaluation. However these changes have not been included in version 3. A revised ASA, incorporating all previously accepted changes should be submitted with the sponson's response.
Sponsor's response: Changes made to the ASA as a result of the initial TGA evaluation for the first nivolumab application were not included in Nivolumab ASA v3 due to timing of the dossier submission for another nivolumab application in December 2015. Nivolumab ASA version 2.2 was approved by the TGA as part of the initial Opdivo MAA on 7 January 2016. The sponsor has provided a copy of the current Opdivo Immune-Related Adverse Reaction (irAR) Management Guide and copies of the two Patient Alert Cards (there are separate Patient Alert Card for patients who are receiving Opdivo as monotherapy and Opdivo in combination with ipilimumab).
RMP Evaluator comment: A revised ASA has been submitted with the previously accepted changes included.
Recommendation 8: The sponsor should also detail any planned changes to the previously accepted educational materials to accommodate the proposed extension of indications.
Sponsor's response: As the safety profile remains unchanged across the tumour types for nivolumab monotherapy, no changes are required to the key messages or irAR management algorithms within the educational materials as a result of the RCC indication. There are no risk minimisation activities or recommendations specific to the RCC indication. The existing risk minimisation (educational) materials will only be updated to include the approved RCC indication and updated pooled monotherapy irAR data (pooled monotherapy safety data updated to include data from Study CA209025). These updates will be aligned to the approved Opdivo PI for the RCC indication as part of this application.
RMP Evaluator comment: The sponsor should provide these updated educational materials to the TGA when available.
Recommendation 9: The evaluator accepts that there may have been changes to the PI as result of previous approvals. The sponsor should ensure that Table 5.1-2 of the ASA reflects the most recently approved PI as well as any proposed amendments as a result of this application.

Sponsor's response: The safety profile of nivolumab monotherapy remains consistent across tumour types and there have been no changes to the safety concerns contained in the Nivolumab EU-RMP. Therefore, there have been no changes made to the risk minimisation wording included in the proposed Opdivo PI for the indications of RCC, classical Hodgkin lymphoma (cHL), and squamous cell cancer of the head and neck (SCCHN). As agreed during the sponsor/TGA teleconference of 17 June 2016, revised Opdivo PI version 3.3 will be submitted to the TGA under separate cover. Based on comments from the clinical evaluator and discussion with the TGA Delegate on 17 June 2016 there are no proposed amendments to Opdivo PI version 3.3 that will impact the risk minimisation wording (compared to Opdivo PI version 3.2).
RMP Evaluator comment: The ASA (version 5) reflects the current PI (version 3.3).
Recommendation 10: The acceptability of the consolidated risk minimisation plan, to be submitted with the sponsor's response, will be evaluated in round 2.
Sponsor's response: The sponsor acknowledges the RMP evaluator's comment.
RMP Evaluator comment: EU-RMP version 6 and ASA version 5 have been considered as part of the round 2 evaluation.

Summary of recommendations

New recommendations (major)

1. The sponsor should update the Summary of Safety Concerns as shown in a specified table of the RMP Round 2 Evaluation Report, to include immune related neurological AEs and a more complete description of the other irAEs known to be associated with nivolumab treatment. These changes should also be captured in the ASA.
2. The sponsor should revise the HCP communication tool to include the RCC indication, and update the information included based on the revised Summary of Safety Concerns. Once revised, the materials should be submitted to the TGA for evaluation, and appended to a revised version of the ASA.
3. The sponsor should revise the Patient Alert Card to include the RCC indication, and update the information included based on the revised Summary of Safety Concerns. In addition, during the revision process the sponsor should give consideration to the clinical evaluator's comments regarding the format of the Patient Alert Card. Once revised, the materials should be submitted to the TGA for evaluation, and appended to a revised version of the ASA.
4. The sponsor should include the planned submission dates for Study CA209401 in the ASA.
5. The EU-RMP states there are two PIPs. The ASA only refers to one PIP. The sponsor should amend the ASA to include reference to both PIPs, and append a copy of the second PIP to the ASA.

New recommendations (other)

1. The sponsor should provide an update on Study CA209234 when it is available, and commit to submitting the interim and final reports to the TGA in the ASA.
2. For completeness, the sponsor should include the ongoing efficacy studies in the ASA.
3. The sponsor should include Study CA209401 in the EU-RMP as it is a global study.

4. The sponsor should clarify whether the study number for the third melanoma combination study listed is correct (listed as Study CA20906, but the RMP evaluator believes this should be '*Study CA209069'*.
5. The annual interim reports of Study CA209401 should be submitted to the TGA for review when available. The sponsor should make a commitment in the ASA to submit the interim and final study reports for this study, as well as the other planned and ongoing studies.

VI. Overall conclusion and risk/benefit assessment

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

The indication proposed (as per sponsor response to TGA questions) is:

> *'Opdivo, as monotherapy is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) after prior therapy in adults'*

Quality

Manufacturing and quality control issues were evaluated during the initial application for registration of the first nivolumab NBE submission.

Nonclinical

Nonclinical and toxicology issues, were evaluated during the initial application for registration of the first nivolumab NBE submission.

Clinical

The clinical evaluator has provided a comprehensive report. Rather than re-presenting background information and clinical data in any detail here, the focus will be on addressing issues raised in that report.

For further details, please see the extract of the clinical evaluation report in Attachment 2.

Clinical evaluator's recommendation

The evaluator was uncertain about benefit/risk balance after the first round evaluation.

After second round, the evaluator concluded:

> *'The evaluator recommends that nivolumab be approved for the indication of: Adult patients with advanced RCC (clear cell) who had received prior anti-angiogenic therapy.'*

Ongoing refinement of the educational/awareness tools of the PI, Patient Alert Card and HCP guide (as recommended in the sections below) are essential to minimise the risks associated with irARs. A multicentre national observational registry would provide information regarding the safety and efficacy of nivolumab outside of clinical trials in the Australian context.

The clinical evaluator has summarised benefits and risks succinctly (see Tables 8 and 9 and clinical findings, above).

Overview of data

Study CA209025

This was the pivotal study. Subjects with advanced RCC with a clear cell component who had received 1 or 2 prior anti-angiogenic therapies for advanced disease were enrolled. Sunitinib and pazopanib were commoner prior therapies. Patients with CNS metastases were excluded. N = 410 were randomised to receive nivolumab 3 mg/kg every 2 weeks IV and n = 411 to receive everolimus 10 mg/day orally. The study was open label. Median duration of treatment was 5.5 months for nivolumab, 3.7 months for everolimus. Minimum follow-up was 14 months.

The primary endpoint was OS. The study was stopped when a pre-planned interim analysis found an advantage in OS for nivolumab. The HR for OS was 0.73 (95% CI 0.57 to 0.93); median OS was 25 months in the nivolumab arm, 19.6 months in the everolimus arm. There was no sign of a plateau for OS, though median OS had only just been reached.

Subgrouping by PD-L1 status did not reveal differences. There was a suggestion the ≥ 75 years subgroup did not benefit from nivolumab (HR 1.23, 95% CI 0.66 to 2.31). Otherwise, all subgroups had an OS benefit with nivolumab.

ORR was 25.1% for nivolumab, 5.4% for everolimus, with median duration of response 12 months in each arm. The PFS HR was 0.88 (95% CI 0.75 to 1.03); median PFS was 4.4 to 4.6 months across arms. There was no independent review of responses.

In both arms, 44 to 46% of subjects were treated beyond progression. 51/179 treated in this way with nivolumab derived 'non-conventional benefit' but the evaluator could not conclude that treatment beyond progression was justified.

Safety outcomes were arguably better in the nivolumab arm, for example drug related Grade 3 to 4 AEs were seen in 18.7% (nivolumab) versus 36.5% (everolimus); SAEs were reported in 48% (nivolumab) versus 44% (everolimus) but drug related SAEs of any grade were seen in 11.6% versus 13.4% respectively. Discontinuations due to study drug toxicity were more common for everolimus (see Attachment 2). The spectrum of nivolumab AEs was similar to that observed in other nivolumab studies. It is possible that pneumonitis was under reported.

There was a suggestion that quality of life was better in patients on nivolumab than in patients on everolimus (see Attachment 2).

Studies CA209003, CA209010 and CA209009

These provided data about nivolumab monotherapy in advanced RCC but not using the proposed dose regimen. For Study CA209010, there were only 54 to 59 subjects per arm, but there was a suggestion that the low dose (0.3 mg/kg every 3 weeks) was not as efficacious as 2 to 10 mg/kg every 3 weeks. For Study CA209003, 1 and 10 mg/kg every 2 weeks dosing produced similar ORRs. For Study CA209009, results were fairly consistent with lower efficacy at 0.3 mg/kg every 3 weeks dosing (see Attachment 2).

There was evidence of a higher rate of hypersensitivity/infusion reactions for the 10 mg/kg arms of Studies CA209010 and CA209009.

Population PK is described in Attachment 2.

Risk management plan

The RMP evaluator considered EU-RMP version 6; date 25 May 2016; Data lock point 18 December 2015; and ASA version 5; 4 July 2016.

The second round RMP evaluation includes major recommendations as follows:

- The sponsor should update the Summary of Safety Concerns as shown in the table [not included here] of the second round RMP evaluation report, to include immune related neurological adverse events and a more complete description of the other irAEs known to be associated with nivolumab treatment. These changes should also be captured in the ASA.
- The sponsor should revise the Health care professional communication tool to include the RCC indication, and update the information included based on the revised Summary of Safety Concerns. Once revised, the materials should be submitted to the TGA for evaluation, and appended to a revised version of the ASA.
- The sponsor should revise the Patient Alert Card to include the RCC indication, and update the information included based on the revised Summary of Safety Concerns. In addition, during the revision process the sponsor should give consideration to the clinical evaluator's comments regarding the format of the Patient Alert Card. Once revised, the materials should be submitted to the TGA for evaluation, and appended to a revised version of the ASA.
- The sponsor should include the planned submission dates for Study CA209401 in the ASA. (This study is described in the RMP evaluation report as a trial of nivolumab plus ipilimumab followed by nivolumab in 1L Stage III (unresectable) or Stage IV melanoma).
- The EU-RMP states there are two paediatric investigation plans (PIP). The ASA only refers to one PIP. The sponsor should amend the ASA to include reference to both PIPs, and append a copy of the second PIP to the ASA.

The CER included detailed consideration of risk mitigation, with many suggestions applying across all uses of nivolumab (that is, not just RCC). The clinical evaluator writes in the CER:

'The sponsor has provided the EU RMP version 6.0 (Dated 25 May 2016) and the ASA version 5 (Dated 30 June 2016) for the Round 2 evaluation. The Nivolumab EU-RMP version 6/ASA Version 5 include the indications for classical Hodgkin's lymphoma (cHL) and squamous cell carcinoma of the head and neck (SCCHN). This results from an agreement between the TGA and the sponsor that the most up to date version of the Nivolumab EU-RMP/ASA (including all indications) will be submitted to the TGA whenever an RMP is required by the TGA. As the TGA cannot generally approve an RMP containing indications that are still under evaluation, '[the sponsor] requests that the cHL and SCCHN specific information in [the] ASA [Version] 5 is disregarded when considering the current application for RCC'.

The clinical evaluator made recommendations to the TGA regarding the RMP safety specification. The broad issues are: SIRS/MODS/MOF; cardiac arrhythmias given the risk of myocarditis; distinguishing neurological from irAEs; and updating 'other' irAEs. These issues are expanded upon below.

The clinical evaluator emphasised the importance of the HCP tool (that is, educational materials directed at clinicians), the patient communication tool (including patient alert card) and the PI/CMI in risk mitigation. Proposed changes related to: adding clinical detail to the HCP tool; adding directions to the PI in the HCP and patient communication tools; displaying the boxed warning on the Health care professional tool; modifying the format of the patient alert card; revising distribution of the Health care professional tool; and revising distribution of the PI.

Recommended conditions of registration

The second round RMP evaluation noted: *'At this time, suggested wording for the conditions of registration cannot be provided due to the recommended amendments to the Summary of*

Safety Concerns and other outstanding issues described above including changes to the HCP communication tool and Patient Alert Card.'

PSUR (January 2016 to July 2016)

This PSUR was received by the TGA on 24 August 2016, thus is not incorporated into any of the evaluation reports. A brief review indicates:

- In total, approximately 31,479 subjects have been exposed to nivolumab in sponsored clinical trials and through the Early Access Program/compassionate use programs from 28 July 2006 through to 3 July 2016.
- Cumulative exposure to nivolumab in a post-marketing setting is > 150,000 person years, across at least melanoma and NSCLC uses.

The following text is extracted from the sponsor document's Executive Summary:

- During the reporting period, the sponsor and ONO pharmaceuticals issued two Dear Healthcare Professional (DHCP) letters in Australia:
  - The first Dear Healthcare Professional (DHCP) letter notified the HCPs that the approved indication for Opdivo in locally advanced or metastatic squamous and non-squamous NSCLC does not include combination with TKIs. SAEs including deaths (1 case of pneumonitis and 1 case of TEN), had been reported in a Novartis sponsored, Phase II, non-randomised trial of nivolumab in combination with an investigational third generation TKI.
  - The second DHCP letter notified HCPs of isolated cases of SAEs in the Northern Hemisphere (including life threatening or fatal myocarditis, myositis and rhabdomyolysis), in patients administered nivolumab plus ipilimumab combination regimen and who had also received an influenza vaccine. The individual benefit-risk decision as to whether to treat a patient with nivolumab plus ipilimumab combination regimen post-influenza vaccination or to advise against influenza vaccination of an already treated patient should be made on a case-by-case basis in consultation with the treating medical oncologist. The sponsor prepared a template letter for the HCP and their patient to provide to their general practitioner or allied HCP so that they are informed of the benefits and risks of therapy and are vigilant of reporting any adverse reactions.
  - The sponsor and ONO Pharmaceuticals issued an Alert for Proper Use of Drug to HCPs in Japan to raise awareness of the incidence of type 1 diabetes mellitus, including early detection and treatment of fulminant type 1 diabetes mellitus, attributable to Opdivo intravenous infusion, 20 mg and 100 mg.
- The Company Core Data Sheet was revised to include a new safety concern of rare, observed cases of Stevens-Johnson syndrome (SJS) and TEN, some with fatal outcome, and described the recommended management guidance for these events. The important identified risk of 'immune related rash' was renamed as 'immune related skin ARs'. Myocarditis, myositis, and rhabdomyolysis were also added as ADRs under 'other immune related ARs' given the biological plausibility of the nivolumab mechanism of action to cause or contribute to autoimmunity and the potential inflammatory nature of myocarditis, myositis, and rhabdomyolysis.

Of peripheral interest:

- To facilitate simultaneous co-administration of nivolumab and ipilimumab, the sponsor has developed a fixed ratio combination drug product at a nivolumab/ipilimumab protein-mass ratio of 1 to 3 in the same vial for the treatment of first line melanoma.

Risk-benefit analysis

Delegate's considerations

Background

Nivolumab is a mAb targeting PD-1; it is one of several registered anti-PD-1 checkpoint inhibitors, the other being pembrolizumab.

Manufacturing and quality control issues, and toxicology issues, were evaluated during the initial application for registration of the first nivolumab NBE submission.

Clinical

The focus here will be on addressing issues raised in the CER.

The proposal to extend use to advanced RCC is broadly acceptable, but the clinical evaluator suggests a *more restrictive indication* than proposed by the sponsor, that is, use only in clear cell RCC and use only after ≥ 1 anti-angiogenic systemic therapy.

The evaluator also makes recommendations about approaches to risk mitigation, encompassing changes to the PI (for example, an expanded black-box warning that focuses more attention on risks of nivolumab monotherapy) and refinements to HCP educational tools and the Patient Alert Card. The evaluator also recommended an Australian nivolumab registry that could provide information on the efficacy and safety of nivolumab outside of the clinical trial setting.

Risk Management Plan (RMP)

The RMP evaluator recommended adjustments to the Summary of Safety Concerns and updating of the HCP tool and Patient Alert Card to reflect use in advanced RCC. There were no major issues arising out of the RMP evaluation report.

Issues

Efficacy in renal cell carcinoma

Efficacy was established in the patient population studied in Study CA209025, using a relevant comparator (everolimus). The clinical evaluator raised some concerns about endpoints reliant on investigator assessment of tumour response (see Attachment 2), as there was no central/independent review of response. The primary study endpoint was OS. ORR might be subject to bias, but the improvement in ORR with nivolumab is consistent with the more incontrovertible gain in survival.

There was no influence of PD-L1 IHC status on outcomes in Study CA209025 (see Attachment 2). From the pivotal study, only 24% of subjects had ≥1% PD-L1 positive cells, and only about 8% had ≥ 10% positivity. A comparison across the sponsor's studies of Opdivo across various cancer types is on available in Attachment 2.

Regarding further exploration of biomarkers to improve the benefit/risk balance of nivolumab (for example, description of EMA requirements in Attachment 2), the TGA would be interested in updates from the sponsor about significant outcomes from this further exploration.

Safety in renal cell carcinoma

Most issues regarding safety and risk mitigation raised by the clinical evaluator are not specific to use in patients with RCC but apply more broadly to all use of nivolumab.

Overall risk-benefit in renal cell carcinoma, and indication

In the clinical evaluation report (see Attachment 2), the clinical evaluator notes that:

1. The inclusion criteria of the pivotal efficacy study specified *'renal-cell carcinoma with a clear-cell component'*. It would be appropriate to limit the indication to this population.
2. The term 'prior therapy' is very broad and may include surgery, radiotherapy or other therapies. The unmet need described by the sponsor in the Clinical Overview is '*advanced RCC after prior systemic therapy*'. A more specific indication may be appropriate, such as that recently approved by the FDA: '*patients with advanced RCC who had received prior anti-angiogenic therapy'.* The evaluator recommends the wording*: 'patients with advanced RCC (clear cell) who had received prior anti-angiogenic therapy'*.

With regard to clear cell specification, it is relevant that 70 to 80% of RCC is clear cell.

The clinical evaluator recommends the following indication:

> *'Adult patients with advanced RCC (clear cell) who had received prior anti-angiogenic therapy'*

The evaluator makes the following additional points:

- The sponsor provided the ORR results of 9 patients with advanced RCC who were treated with 1 mg/kg or 10 mg/kg Q2W of nivolumab and who had not received prior anti-angiogenesis therapy to support the use in this population.
- No information was presented to support the use in patients with non-clear cell RCC although the sponsor speculated that due to the unique mechanism of action, nivolumab may be effective in this population. The sponsor also indicated that a study of nivolumab in patients with non-clear cell RCC in currently ongoing.
- 'Prior therapy' may be interpreted as prior surgery, with nivolumab then used as first-line systemic therapy.

This is further discussed in Attachment 2.

Safety in all uses: risk mitigation

The clinical evaluator writes: *'Delays in appropriate care, and worse outcome, may result from lack of awareness of the unique side effect profile of checkpoint inhibitors. The EMA has sought to address this lack of familiarity through the use of a Patient Alert Card (including advice for both patient and medical practitioners providing emergency care) and physician education packages. The evaluator strongly recommends that the TGA also adopt this approach.'*

The clinical evaluator recommends addressing lack of familiarity with irAEs by:

1. Amending the PI boxed warning.
2. Ensuring appropriate clinical detail is provided in the PI and/or HCP tool ('immune related adverse reaction management guide'.

On this point, the clinical evaluator argues that the PI should include more detail about recognition and management of irARs, or that at the very least more detail should be included in the HCP tool. A related recommendation is to be more prescriptive about laboratory monitoring.

The clinical evaluator also considers that *advice regarding use of non-corticosteroid immunosuppressive agents* to treat irAEs could be strengthened. One possibility is to refer to specific agents in the HCP irAR management guide.

Note, the Investigator's Brochure for Study CA209025, version 14 was considered by the evaluator to provide a sufficient level of detail; it is included as a paper for Advisory Committee on Prescription Medicines (ACPM).[10]

3. Ensuring appropriate emergency care advice in a Patient Alert Card.
4. Targeting oncologists, oncology nurses and pharmacists, as well as GPs, emergency medicine specialists and hospital clinicians, in post-market education.

Safety in all uses: TEN/SJS, myositis, myocarditis, rhabdomyolysis

The sponsor's request to update the PI to reflect information about TEN/SJS, myositis, myocarditis and rhabdomyolysis is being assessed separately (but is noted in the CER (see Attachment 2)).

Safety in all uses: discontinuation after Grade 4 endocrinopathies

In the CER the following is noted (see Table 14, below).

Table 14. Excerpt from the CER, comment on rationale for discontinuation after Grade 4 endocrinopathies in the PI

Adverse Effects: Description of selected adverse reactions, Immune Related Endocrinopathies	Endocrinopathies manifesting as hormonal deficiency can be managed by hormonal replacement. The PI advises that nivolumab treatment be ceased if Grade 4 endocrinopathies occur although the treatment may be resumed for Grade 3 endocrinopathies in which hormone replacement therapy has been effective in controlling the manifestations of the endocrinopathy. The sponsor has been asked to provide the rationale for treatment discontinuation in Grade 4 endocrinopathies as a blanket statement. See TGA Clinical Questions.
Sponsor's comment	Please see response to question.
Evaluator's comment	The response to the question has not provided the requested rationale.

Safety in all uses: myasthenia gravis-like syndromes

Myasthenia gravis-like syndromes have been reported with checkpoint inhibitors, as discussed by Naidoo et al.[11]

Events have occurred with ipilimumab and with combined PD-1/CTLA-4 pathway inhibition, including a case with nivolumab + ipilimumab in small cell lung cancer.[12]

The Yervoy PI includes a Precaution mentioning myasthenia gravis-like symptoms.

The proposed nivolumab PI version 3.3 refers in a table to myasthenic syndrome as rare, but in the nivolumab monotherapy column. There is also reference to the syndrome in the last paragraph before 'Dosage and Administration'.

Given that myasthenic syndrome can be life-threatening (see cited report), the PI should refer to this possibility in the Precautions section and also provide dose modification / cessation advice.

10 The ACM was established in January 2017, to encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM).
11 Naidoo et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Annals of Oncology (2015) 26 (12): 2375-2391).
12 Loochtan et al. Myasthenia gravis associated with ipilimumab and nivolumab in the treatment of small cell lung cancer. Muscle and Nerve 2015; 14 May 2015.

Loochtan et al., comment that ipilimumab may play an important causative role and that the possible role of nivolumab is unclear, but (a) the nivolumab PI version 3.3 already notes that myasthenic syndrome may occur with nivolumab monotherapy; and (b) it seems very plausible that with combination use, additional blockade of the PD-1 pathway will increase the risk of occurrence and/or increase the risk of a severe event relative to use of ipilimumab alone.

The US PI for atezolizumab (a PD-L1 inhibitor) includes a warning to permanently discontinue in the event of myasthenic events.

Safety in all uses: registry

The clinical evaluator recommends a national multicentre observational registry in Australia (see Attachment 2).

There are many ongoing sponsor and investigator initiated trials of nivolumab in Australia and globally. Assessment of rare events can be made by pooling safety findings across trials. There have been no TGA-specific registry requirements for other checkpoint inhibitors to date.

The Delegates preliminary view is that no registry is required.

Proposed conditions of registration

RMP related conditions of registration are likely to be necessary; see above.

The clinical evaluator writes: *'The additional analyses of the value of biomarkers to predict the efficacy of nivolumab and/or nivolumab + ipilimumab combination therapy now includes two studies of patients with advanced RCC, CA209025 and CA209009. These reports should be provided to the TGA as they become available.'*

A recommendation about a registry is discussed above.

Proposed action

The RCC indication is approvable. The wording of the indication is for discussion at ACPM.

Although issues regarding risk mitigation raised by the clinical evaluator extend beyond use in RCC, they also apply to use in RCC, so they need to be resolved to the satisfaction of the Delegate prior to approval of the application.

Request for ACPM advice

1. Should the indication be restricted to clear cell RCC (as opposed to RCC)? Should the indication be restricted to patients with prior anti-angiogenic therapy (as opposed to prior therapy)?
1. Should the boxed warning be modified to focus more on risks of monotherapy use of nivolumab?
2. What are the ACPM's views regarding an appropriate level of clinical detail in the PI and healthcare professional tool regarding detection and management of irAEs?
3. Does the ACPM have any suggestions about improvements to the patient alert card format or content?
4. Does the ACPM consider that the risk of myasthenia gravis-like syndromes merits a specific Precaution, or mention within a specific 'Neurological irAEs' Precaution?
5. Is there sufficient evidence to support a Precaution about 'systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), and multiple organ failure (MOF)'?

Some questions were also directed towards the sponsor (see 'Questions for sponsor, below). A response to the second 'Question to the sponsor' may help inform ACPM's response to Question 6 above.

Questions for sponsor

1. Is there any suggestion of decreased efficacy in the elderly for nivolumab across other major studies (for example in melanoma, NSCLC)?
2. Is there any evidence of a higher risk of SIRS/MODS/MOF with combination use of nivolumab/ipilimumab?

Response from sponsor

The sponsor provides the following comments in relation to questions submitted to the ACPM.

Sponsor's responses to questions to ACPM

1. *'Should the indication be restricted to clear cell RCC (as opposed to RCC)? Should the indication be restricted to patients with prior anti-angiogenic therapy (as opposed to prior therapy)?'*

The optimal systemic therapy for non-clear cell renal cell carcinoma remains unclear as limited high-quality clinical efficacy and safety data exist in non-clear cell RCC compared to clear cell RCC. Therefore, in general, treatment of non-clear cell RCC mirrors that of clear cell RCC.[13]

Currently TGA-approved indications for advanced RCC are not restricted by histology even when no, or very limited, study results were available for patients with non-clear cell RCC to support registration. Given the lack of other second-line treatment options for which there is strong evidence of a clinical benefit in non-clear cell RCC and the lack of clinical rationale suggesting that the activity of nivolumab would be limited to the clear-cell population, the sponsor proposes to retain an indication unrestricted by histology, consistent with regulatory precedent.

The sponsor has noted the clinical evaluator's concern that the proposed term 'prior therapy' could be misinterpreted to mean any therapy including surgery and radiotherapy. For clarity, and to address this concern, the sponsor proposes to amend the indication to specify 'prior systemic therapy'. This is also aligned with currently TGA-approved RCC indication statements.

For these reasons, the sponsor proposes the following amendment to the indication:

> *'Opdivo, as monotherapy is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) after prior systemic therapy in adults.'*

In line with the above, the sponsor also proposes amendments to the 'Clinical Trials' section, to specify that 'All patients had RCC with clear cell histology component' in Study CA209025.

In summary, the sponsor believes that the indication for nivolumab should be aligned with other approved medicines in Australia based on similar clinical trial evidence, thus facilitating a consistent interpretation of RCC indications by prescribers.

2. *'Should the boxed warning be modified to focus more on risks of monotherapy use of nivolumab?'*

13 Valenca L et al. Non-clear cell non–clear cell renal cell carcinoma, part 2: therapy. Clinical Advances in Hematology & Oncology. 2015;13(6):383-91.

The sponsor strongly disagrees with the clinical evaluator's recommendation that the PI boxed warning should be broadened to include the risks of nivolumab monotherapy as the nivolumab monotherapy safety profile has remained unchanged relative to that of the combination with nivolumab and ipilimumab (combination therapy).

During the evaluation of the initial registration of Opdivo the Delegate concluded that, *'Relative to nivolumab monotherapy, there is a major step-up in toxicity with addition of ipilimumab to the regimen'* and requested a Boxed Warning to reflect this.

With increased usage and exposure levels of nivolumab monotherapy, the event count of AEs has increased as would be expected. However, it is important to note that there has been no change in the event frequency for irARs since the initial approval of nivolumab in Australia (14 January 2016), as illustrated by Table 15, below.

During this period, the cumulative exposure to nivolumab in clinical trials, early patient access programs, and post-market use has increased from 38,556 to 68,069; this analysis is therefore based on the largest available safety database for an immuno-oncology agent.

Table 15. Cumulative event frequency of Grade 1 to 5 selected irARs from clinical trials by Month (2016)

irARs	Jan (n=4796)	Feb (n=4871)	Mar (n=4945)	Apr (n=5073)	May (n=5189)	Jun (n=5291)	Jul (n=5417)	Aug (n=5554)
Nivolumab Monotherapy								
Pneumonitis	3.94%	4.00%	4.11%	4.10%	4.14%	4.12%	4.19%	4.07%
Colitis	13.30%	13.32%	13.39%	13.36%	13.51%	13.55%	13.55%	13.43%
Hepatitis	10.11%	10.39%	10.78%	10.82%	10.95%	11.42%	11.52%	11.56%
Renal	2.44%	2.40%	2.39%	2.37%	2.35%	2.31%	2.29%	2.43%
Endocrinopathies	10.95%	11.23%	11.67%	11.59%	11.93%	12.00%	12.02%	11.99%
Skin	35.32%	35.35%	35.49%	35.50%	36.08%	36.02%	36.13%	35.97%
irARs	**Jan (n=2107)**	**Feb (n=2166)**	**Mar (n=2227)**	**Apr (n=2302)**	**May (n=2395)**	**Jun (n=2465)**	**Jul (n=2563)**	**Aug (n=2643)**
Combination Therapy (Nivolumab+Ipilimumab)								
Pneumonitis	6.79%	6.93%	7.05%	7.12%	7.01%	6.86%	6.71%	6.55%
Colitis	39.82%	39.70%	39.47%	39.44%	38.41%	38.09%	37.46%	37.12%
Hepatitis	38.21%	38.41%	38.35%	38.44%	37.66%	37.04%	36.91%	36.40%
Renal	6.55%	6.46%	6.65%	6.82%	6.76%	6.53%	6.44%	6.32%
Endocrinopathies	36.88%	37.72%	38.39%	38.05%	38.62%	38.17%	37.81%	37.65%
Skin	76.51%	76.78%	77.50%	76.85%	75.49%	74.81%	74.05%	72.99%

Critically, each irAR frequency remains substantially lower for nivolumab monotherapy compared to combination therapy, therefore retaining a distinct difference.

Relevant precautions for both nivolumab monotherapy and combination therapy are already captured prominently in the PI.

With the large increase in cumulative exposure to nivolumab, there have been additional cases of less frequent AEs in recent months (for example, SJS, TEN, myositis, myocarditis, rhabdomyolysis) with both nivolumab monotherapy and combination therapy (see Table 16, below).

Table 16. Frequency of recently identified AEs observed in clinical trials (including Early Patient Access)

AE	Nivolumab Monotherapy	Combination Therapy (Nivolumab+Ipilimumab)
Stevens-Johnson syndrome	0.03%	0.03%
Toxic epidermal necrolysis (TEN)	0.01%	0.03%
Myositis	0.06%	0.2%
Myocarditis	0.01%	0.2%
Rhabdomyolysis	0.02%	0.1%

For each of these events, the frequency observed in clinical trials was higher with combination therapy use compared to nivolumab monotherapy, consistent with that observed with the irAR profiles discussed above.

Sponsor pharmacovigilance practices ensure that all emerging safety concerns are assessed and appropriately incorporated into labelling updates. The assessment of these events resulted in sponsor-initiated labelling updates globally, and included the PI (April 2016 and September 2016). This does not represent a change in the nivolumab monotherapy safety profile; rather, it further characterises the safety profile with respect to irARs.

The Delegate notes the 3 Periodic Benefit Risk Evaluation Reports (PBRERs) submitted to TGA since initial registration. All 3 PBRERs include similar AEs commonly reported during the data lock points from 4 July 2014 to 3 July 2016, and support the unchanged safety profile of nivolumab monotherapy relative to the combination therapy.

The sponsor considers the clinical evaluator's recommendation to modify the boxed warning to be arbitrary given the absence of TGA guidance on required evidence to trigger a boxed warning.

Further, as noted by the Delegate, the only boxed warning globally for any immuno-oncology therapy is for Yervoy in the United States and Australia. For combination therapy, the only boxed warning is in Australia.

The sponsor notes the clinical evaluator's concern that the current boxed warning could mislead clinicians that fatal outcomes only occur with combination therapy. Although the current boxed warning already states that life-threatening irARs are seen with both nivolumab monotherapy and combination therapy and that they are more serious and more frequent with the combination therapy, the sponsor proposes to rearrange this information as the opening statement of the boxed warning for greater prominence. The outcomes of irARs for both the monotherapy and the combination therapy are already described in the 'Precautions' in the approved PI:

'Warning: Immune related adverse reactions with Opdivo and Yervoy (ipilimumab) combination therapy.

More frequent and more serious immune-related adverse reactions are seen with OPDIVO and Yervoy combination therapy than with the use of single agent nivolumab or ipilimumab. Potentially life-threatening immune-related adverse reactions including pneumonitis, hepatitis, diarrhoea/colitis, skin adverse reactions, hypophysitis and thyroid dysfunction as well as immune related adverse reactions in other organ system have been observed.

Physicians should consult the Yervoy product information prior to initiation of Opdivo in combination with Yervoy. 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.

Early diagnosis and appropriate management are essential to minimise life-threatening complications (see Precautions, Adverse Effects and Dosage and Administration).'

The sponsor asserts that the PI should reflect an accurate sense of proportion in relation to the relative risk between nivolumab monotherapy and combination therapy and believes the proposed amendments to the current boxed warning fully address this clinical evaluator concern.

3. *'What are the ACPM's views regarding an appropriate level of clinical detail in the PI and healthcare professional tool regarding detection and management of irAEs?'*

The sponsor notes the clinical evaluator's recommendation that the PI and HCP Tool should include more details from the nivolumab Investigator Brochure. The sponsor contends that the current PI and HCP tool are sufficiently detailed to provide HCP with the

necessary guidance to make informed clinical care decisions regarding irAR detection and management, while ensuring that the HCP has enough flexibility to tailor the management of irARs to the patient's specific needs.

Several reasons support this position:

Firstly, the purpose of the Investigational Brochure is to provide HCPs with information on an investigational product while the efficacy and safety profile is still being established. The management algorithms for nivolumab were originally developed based on early Phase I clinical experience. Many of the recommendations were empiric (based on mechanism of action and understanding of ipilimumab toxicity). The algorithms are intended to convey general principles around delaying or discontinuing treatment in the presence of significant immune-mediated toxicity, and treating symptoms with immunosuppressants. Given the rarity of some of these irARs, the sponsor cannot state with certainty that these specific measures are required for adequate management.

Secondly, through clinical trial participation over the past 10 years and the availability of registered immunotherapies since 2011, 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 continue to be developed throughout centres in Australia.

Thirdly, the Opdivo HCP tool already details significant management and follow-up recommendations for each potentially affected organ system by grade of severity of each irAR. The approved PI already provides guidance for the recognition and management of irARs under the sections 'Precautions and 'Dosage and Administration'. The 'Precautions' section describes the clinical presentation of individual irARs, advice regarding management, specific laboratory monitoring, and treatment modifications. Treatment modifications are further presented in a table in the section 'Dosage and Administration' Recommended Treatment Modifications for Opdivo.

The use of immunosuppressive therapy is driven by clinical judgement to ensure appropriate titration, duration of treatment, and withdrawal of therapy to meet a patient's individual circumstance. Overly prescriptive advice could inadvertently result in inappropriate treatment of a patient's irAEs. The current PI recommendation allows for clinical judgement to be exercised, while not precluding alternative options. This rationale has been previously discussed with the TGA Delegates, as a result of which generic recommendations have been retained in the PI.

Finally, the sponsor agrees with the RMP evaluator's assessment of the current Opdivo HCP Tool that 'the format and current content of the material available for HCPs adequately addresses the intended safety concerns. It also provides suitable instructions on how to treat AEs, and the relevant information regarding dosage adjustments.' The only update requested by the RMP evaluator is to align with the updated safety concerns, which the sponsor is addressing.

4. *'Does the ACPM have any suggestions about improvements to the Patient Alert Card format or content?'*

The sponsor agrees to the clinical evaluator's recommendations for improvements to the Patient Alert Card. A smaller, streamlined format of the Patient Alert Card is proposed, and addresses these recommendations.

5. *'Does the ACPM consider that the risk of myasthenia gravis-like syndromes merits a specific Precaution, or mention within a specific 'Neurological irAEs' Precaution?'*

The sponsor proposes to amend the PI to ensure easy identification and management of the risk of myasthenia gravis-like syndromes:

In sections 'Precautions' and 'Adverse Events', creation of a distinct category of 'immune related neurological adverse reactions' to include the AEs of demyelination, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, autoimmune neuropathy (including facial and abducens nerve paresis) and encephalitis.

In section 'Dosage and Administration', include guidance on management of myasthenic syndrome/myasthenia gravis as a separate event under the category 'immune-related neurological adverse reactions'.

6. *'Is there sufficient evidence to support a Precaution about 'SIRS/MODS/MOF'? Is there any evidence of a higher risk of SIRS/MODS/MOF with combination use of nivolumab/ipilimumab?'*

The sponsor has assessed the events of SIRS/MODS/MOF reported in the nivolumab clinical trials program and in post-marketing use and has concluded that these are not safety concerns for nivolumab monotherapy or combination therapy. The sponsor will continue to monitor AEs of SIRS/MODS/MOF as part of routine pharmacovigilance. Continuous safety monitoring will ensure that updated safety information is available in a timely manner and that any future changes to the benefit-risk profile of nivolumab are appropriately reported and managed. This conclusion is based on a cumulative search of the Corporate safety database (AWARE) through 3 July 2016 (Data lock point of the last PBRER submitted to TGA) to identify cases from all sources (serious clinical trials (Phase I to III; Phase IV)), solicited, literature clinical trials, literature post marketing, and spontaneous) where nivolumab was considered a suspect or interacting drug and at least 1 of the reported AE terms in the case was mapped to the preferred terms of SIRS and Organ Failure or MODS using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. The results and sponsor assessments follow.

SIRS is a multifaceted pathophysiological dysregulated inflammatory response to a range of noxious stimuli that may be infectious (sepsis or septic shock) or non-infectious (such as adrenal insufficiency, pancreatitis, anaphylaxis, thromboembolism, burns, trauma, ischemia, complications of surgery, complicated aortic aneurysm, cardiac tamponade, drug overdose, haemorrhage, and so on). The clinical criteria are two or more abnormalities in temperature, heart rate, respiratory rate, or white blood cell count. Thus, the SIRS criteria are a component of clinical parameters reported with multiple diverse conditions with multiple aetiologies. They are a cluster of non-specific criteria that may simply reflect an appropriate host mechanism.

With the link between inflammation and cancer well established, although the mechanism by which cancer induces both local and systemic inflammatory responses is yet to be fully elucidated, there is a suggestion that the SIRS pathophysiology could be related to the disease itself.

An expert scientific task force convened by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine between 2014 and 2015 noted the limitations of previous definitions, and the inadequate specificity and sensitivity of the SIRS criteria.[14] The sponsor agrees with this view.

From the search described above, 13 cases reported a SAE of SIRS. Of the 13 cases, 7 patients received nivolumab monotherapy and 6 received combination therapy. Event outcomes were reported as recovered/resolved (5), recovered/resolved with sequelae (2), recovering/resolving (1), not recovered/not resolved (1), unknown (4). There were no fatal outcomes.

14 Seymour C et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):762-74.

All available information in the 13 cases were independently and comprehensively medically reviewed by the sponsor, taking into account available information on relevant aspects of the specific case, association with underlying disease, biologic plausibility, and presence of a more likely aetiology.

An aggregate review of the currently available nivolumab data found insufficient information to confirm a causal association between nivolumab and SIRS. This assessment is further confounded by the lack of specificity in the diagnostic criteria for SIRS. Therefore, the sponsor deems that SIRS is not a safety concern for nivolumab monotherapy or combination therapy.

The sponsor notes that the clinical evaluator has referred to an American Society of Clinical Oncology poster presentation as additional cases of SIRS that have been reported. This study included a small sample size that was limited to 1 institution, had no comparator, and provided conclusions on PD-1 targeted therapy which were not specific to nivolumab. The SIRS criteria used by the investigators also included hypotension and organ failure, which are not part of the SIRS clinical criteria described above. These cases are not captured in the sponsor's Corporate safety database.

MODS/MOF is a syndrome in which more than one organ system fails. The pathophysiology is not completely understood but there is evidence of initiation of a chain of events that result in activation of several endogenous metabolic pathways, which results in an inflammatory response that can lead to organ failure. Multiple precipitating factors (including infection, inadequate perfusion, hypermetabolism, soft-tissue and bone injury, and inflammatory processes such as pancreatitis) through a common final pathway result in simultaneous organ failure in several organs, most commonly the lungs, kidneys, gastrointestinal tract, and brain. Patient factors such as elderly age, male gender, and medical co-morbidities also play a role. Sepsis is a common cause. It has been suggested that there is a continuous process of varying levels of organ function designated as MODS, further complicated by variations in the definition of organ failure. MODS/MOF is an inherent clinical presentation of underlying disease progression in oncology patients with advanced malignancy.

From the search described above, 46 cases reported an SAE of MODS and 1 case reported an SAE of Organ Failure. Of the 47 cases, 40 patients received nivolumab monotherapy and 7 received combination therapy. Event outcomes were reported as fatal (35 MODS (30 nivolumab monotherapy and 5 combination therapy, reflective of greater exposure numbers with nivolumab monotherapy)), not recovered/not resolved (3), recovered/resolved (2), and unknown (7).

The sponsor assessed all the cases providing clinical assessment, taking into account available information on relevant aspects of the specific case, association with underlying disease, biologic plausibility, and presence of a more likely aetiology. In all 46 cases, causality was attributed to underlying disease progression and not nivolumab monotherapy or combination therapy.

Responses to questions directed to the sponsor

1. *'Is there any suggestion of decreased efficacy in the elderly for nivolumab across other major studies (for example in melanoma, NSCLC)?'*

No consistent evidence of decreased efficacy in the elderly for nivolumab has been observed. Marginally improved or slightly lower survival or response rates were noted in patients 75 years of age or older across tumour types (see Table 3 below summarising the findings for melanoma Study CA209067, squamous NSCLC; Study CA209017, non-squamous NSCLC, Study CA209057; and RCC, Study CA209025). As with the RCC study, the nivolumab studies conducted for melanoma and NSCLC have a very small sample size

of patients that are ≥ 75 years old, which limits the interpretation of these results in the elderly.

Table 17. Survival and response rates in nivolumab subjects ≥ 75 years old: Studies in melanoma, NSCLC, and RCC tumour types

Efficacy Endpoint	Melanoma Study CA209067[3] (N=39)	SQ NSCLC Study CA209017[4] (N=29)	NS NSCLC Study CA209057[5] (N=43)	RCC Study CA209025[6] (N=34)
Overall Survival - Unstratified Hazard Ratio (95% CI)	--	1.85 (0.76, 4.51)	0.90 (0.43, 1.87)	1.23 (0.66, 2.31)
Objective Response Rate ORR unweighted difference (95% CI)	43.6% 16.3% (-4.1, 35.2)	--	--	--

3) Larkin J, et al. Efficacy and safety in key patient subgroups of nivolumab alone or combined with ipilimumab versus ipilimumab alone in treatment-naive patients with advanced melanoma (Checkmate 067). Oral Presentation at European Cancer Congress, 25-29-Sep-2015, Vienna, Austria.
4) Brahmer J, et al. (Supplementary appendix to:) Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373:123-35.
5) Borghaei H, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015; 373(17):1627-39.
6) Motzer R, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015; 373(19):1803-13.

2. *'Does the ACPM consider that advice in the PI about discontinuation of nivolumab if Grade 4 endocrinopathies occur is appropriate?'*

The sponsor recommends that any Grade 4 immune related toxicities lead to permanent discontinuation of nivolumab. This recommendation is not specific to endocrinopathies. Per Common Terminology Criteria for Adverse Events (CTCAE) grading, these events are life-threatening in nature and therefore the sponsor feels it is in the best interest of the patient to be discontinued from therapy in this clinical scenario as the risk overweighs the benefit of continued therapy.

3. *'Does the ACPM consider that a nivolumab-specific registry is required to gather additional data relating to efficacy and safety across all uses of the product?'*

The sponsor concurs with the Delegate's comments *'There are many ongoing sponsor- and investigator-initiated trials of nivolumab in Australia and globally. Assessment of rare events can be made by pooling safety findings across trials. There have been no TGA-specific registry requirements for other checkpoint inhibitors to date and that preliminary view is that no registry is required'.*

The sponsor disagrees that a nivolumab specific registry is required. All nivolumab approved indications in Australia for melanoma, squamous cell NSCLC and non-squamous cell NSCLC have been based on robust Phase III clinical trial data, as is the current application for RCC. The TGA has evaluated nivolumab data in over 3000 patients to date. The TGA approved indications are consistent with globally approved indications, making all post-marketing data and pharmacovigilance measures in place globally relevant and applicable to Australia. The nivolumab safety database is the largest of any immuno-oncology therapy and is shared with the TGA as part of routine pharmacovigilance processes. Further, the comprehensive and continuing global nivolumab development program across tumour types continues to inform that there are no changes in safety across tumours.

Sponsor's conclusion

The sponsor notes the Delegate's recommendation for an amended indication and requests the following:

> *'Opdivo, as monotherapy is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) after prior systemic therapy in adults.'*

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), resolved to recommend to the TGA Delegate of the Secretary that taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Opdivo concentrate solution vial containing 40 mg in 4 mL (10 mg/mL) and 100 mg in 10 mL (10 mg/mL) of nivolumab to have an overall positive benefit–risk profile for the proposed indication:

> *'Opdivo, as monotherapy is indicated for the treatment of adult patients with advanced clear cell renal cell carcinoma (RCC) who had received prior antiangiogenic therapy'.*

Opdivo is already approved for the following indications:

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

In making this recommendation the ACPM:

- noted that Opdivo demonstrated reasonable efficacy and safety for the treatment of patients with clear cell renal cell carcinoma who had received prior antiangiogenic therapy.

Proposed conditions of registration

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

Specific Advice

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

1. *Should the indication be restricted to clear cell RCC (as opposed to RCC)? Should the indication be restricted to patients with prior anti-angiogenic therapy (as opposed to prior therapy)?*

The ACPM noted that inclusion criteria from pivotal efficacy study mandated clear cell RCC and patients had been treated with one or two lines of antiangiogenic therapy. Additionally clinical evaluator recommended the following wording for indication: *'Adult patients with advanced RCC (clear cell) who had received prior anti-angiogenic therapy'*. The committee agreed with indication as suggested by clinical evaluator.

2. *Should the boxed warning be modified to focus more on risks of monotherapy use of nivolumab?*

The ACPM agrees with clinical evaluator that boxed warning in the PI should be modified to focus on risks of monotherapy use of nivolumab.

The ACPM noted the sponsor's proposed modifications to the boxed warning. The ACPM also noted that irAEs can occur late in the treatment course for nivolumab monotherapy and that the PI should communicate this fact.

3. *What are the ACPM's views regarding an appropriate level of clinical detail in the PI and healthcare professional tool regarding detection and management of irAEs?*

The ACPM was of the view that the HCP tool has more details regarding detection and management of irAEs and considered this to be appropriate.

4. *Does the ACPM have any suggestions about improvements to the Patient Alert Card format or content?*

The ACPM agreed with the clinical evaluator's view that Patient Alert Card was overly detailed. The committee also agreed with the suggestions from clinical evaluator for a smaller streamlined format.

5. *Does the ACPM consider that the risk of myasthenia gravis-like syndromes merits a specific Precaution, or mention within a specific 'Neurological irAEs' Precaution?*

The ACPM noted that the sponsor proposed to amend PI in sections 'Precautions' and 'Adverse Events' to include these AEs under 'Immune related neurological adverse reactions' and agreed with these suggested changes.

6. *Is there sufficient evidence to support a Precaution about 'SIRS/MODS/MOF'?*
Note: some questions were also directed towards the sponsor, see Attachment 2[not in this AusPAR]. A response to the second 'Question to the sponsor' may help inform ACPM's response to Question 6 above.

The committee considered that there is insufficient evidence to support precaution. The ACPM noted that the number of SIRS reviewed by sponsor is insufficient to make a causal linkage and the based on the data available from MODS/MOF cases, these events could be attributed to underlying disease progression rather than nivolumab therapy.

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

The committee advised that a registry to gather additional data relating to efficacy and safety across all uses of the Opdivo would be beneficial and provide a tool to identify post-market events. The committee acknowledged that other methodologies exist to identify post-market events.

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.

Outcome

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

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

The full indications are now:

'Opdivo is indicated for:

- *As monotherapy for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma*
- *In combination with Yervoy (ipilimumab) for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH).*

- *As monotherapy for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy.*
- *As monotherapy for the treatment of locally advanced or metastatic non squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK after targeted therapy.*
- *As monotherapy for the treatment of patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy in adults.'*

Specific conditions of registration applying to these goods

· Implement the Opdivo European Union Risk Management Plan (EU-RMP), version 6, dated 25 May 2016; DLP 18 December 2015, and Australian Specific Annex (ASA) version 6; 20 September 2016 and any updates accepted by the TGA's RMP Evaluation Section.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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