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 2019

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>.

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- 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.

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Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASR	Age standardised rate
BIRC	Blinded independent review committee
BMS	Bristol-Myers Squibb (the sponsor)
BOR	Best overall response
BSC	Best supportive care
$C_{avg,ss}$	Time-averaged serum concentration at steady state
CI	Confidence interval
cHL	Classical Hodgkin's lymphoma
CL	Clearance
CR	Complete response
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DFS	Disease free survival
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency (EU)
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQoL – 5 dimension questionnaire
ESMO	European Society of Medical Oncology
EU	European Union
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice

Abbreviation	Meaning
HR	Hazard ratio
ICD	International Classification of Diseases (World Health Organization_
Ig	Immunoglobulin
IV	Intravenous
L	Litre(s)
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NA	Not applicable
Nab	Neutralising antibody
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
NSQ	Non squamous cell
OESI	Other events of special interest
ORR	Objective response rate
OS	Overall survival
PBS	Pharmaceutical Benefits Scheme
PD-1	Programmed death-1
PD-L1	Programmed death-1 ligand
PD-L2	Programmed death-2 ligand
PFS	Progression free survival
PI	Product Information
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)

Abbreviation	Meaning
PR	Partial response
PSP	Pediatric Study Plan (FDA)
Q2W	Every 2 weeks
QoL	Quality of Life
RCC	Renal cell carcinoma
RECIST	Response evaluation criteria in solid tumours
RMP	Risk management plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
SCLC	Small cell lung cancer
SCS	Summary of Clinical Safety
SD	Stable disease
SUR	Safety update report
TGA	Therapeutic Goods Administration
TSH	Thyroid stimulating hormone
UC	Urothelial cancer
ULN	Upper limit of normal

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	6 February 2018
Date of entry onto ARTG:	9 February 2018
ARTG numbers:	AUST R 231867; AUST R 231868
, *Black Triangle Scheme*	No
Active ingredient:	Nivolumab
Product name:	Opdivo
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd PO Box 1080 Mt Waverley VIC 3149
Dose form:	Concentrate solution for intravenous (IV) infusion
Strengths:	40 mg in 4 mL (10 mg/mL); 100 mg in 10 mL (10 mg/mL)
Container:	Vial
Pack size:	1 vial per pack
Approved therapeutic use:	*Urothelial Carcinoma* *Opdivo, as monotherapy is indicated for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy. The approval of this indication is based on objective response rate and duration of response in a single arm study.*
Route of administration:	Intravenous (IV) infusion
Dosage:	The recommended dose of Opdivo as a monotherapy is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Treatment must be initiated and supervised by specialist physicians experienced in the treatment of cancer. Opdivo infusion must not be administered as an intravenous push or bolus injection. Dose escalation or reduction is not recommended. For further details, including guidelines for permanent discontinuation or withholding of doses, please see the current Product Information (PI).

Product background

This AusPAR describes the application by Bristol-Myers Squibb Australia Pty Ltd (the sponsor) to extend the indications to register Opdivo (nivolumab) concentrate for intravenous (IV) infusion for the following indication:

> *Opdivo, as monotherapy, is indicated for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy.*

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody (MAb) which binds to programmed death-1 (PD-1) receptor and blocks its interaction with programmed death ligands 1 (PD-L1) and 2 (PD-L2).

The currently approved formulation for Opdivo is a concentrated solution for IV injection in two approved strengths (100 mg/10 mL and 40 mg/4mL). No changes are being proposed to the dosage form or strengths. No new dosage forms or strengths are being proposed.

Urothelial carcinoma (also known as urothelial cell carcinoma, transitional cell carcinoma of the urinary tract, or urothelial bladder cancer) is one of the most commonly occurring genitourinary malignancies. Urothelial carcinoma is the most common type of bladder cancer and accounts for 90% of cases.[1] Bladder cancer occurs more commonly in patients over the age of 60 than in younger patients and significantly more commonly in men than in women. The estimated relative survival rate for persons with bladder cancer using Australian data from 2007 to 2011 was approximately 53%.**Error! Bookmark not defined.**

There is no published literature describing the current Australian standard of care in patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy.

In Australia, neither paclitaxel nor docetaxel have been approved by the Therapeutic Goods Administration (TGA) for the treatment of urothelial carcinoma. Therefore, the use of these agents for the second-line treatment of patients with urothelial carcinoma after prior platinum therapy is considered to be 'off-label'. In Australia, vinflunine is the only TGA approved medicine for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen. The approved indication for vinflunine is consistent with the proposed extension of indication for nivolumab, and both medicines are considered to target the same patient group.

It is noted that TGA approval of vinflunine was based on a confirmatory Phase III study with a controlled treatment arm (best supportive care (BSC)). The current submission to extend the indications of nivolumab to include patients with urothelial carcinoma includes no confirmatory Phase III study comparing nivolumab with a controlled treatment arm. Based on the TGA approval for vinflunine it is considered that this medicine would be the most appropriate control treatment regimen for nivolumab in the proposed patient population. In the absence of a vinflunine control treatment arm, a control treatment arm consisting of placebo or best standard of care might be appropriate if supported by an acceptable justification.

The sponsor's rationale for the submission is based on 'unmet medical need' for the treatment of patients with advanced or metastatic urothelial carcinoma in the platinum-refractory setting. The condition is serious with significant morbidity, mortality and limited treatment options.

[1] Jemal A, et al. Global cancer statistics. *CA Cancer J Clin*. 2011; 61: 69–90.

While the sponsor's rationale is considered to be acceptable, vinflunine is approved in Australia for treatment of a patient population with urothelial carcinoma consistent with that for which the sponsor is seeking approval for nivolumab.

Regulatory status

Australian regulatory history

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

This is the first application from the sponsor to extend the indications of nivolumab to include the proposed usage in patients with urothelial carcinoma.

Currently approved indications

At the time of submission, Opdivo nivolumab had been approved for the following indications:

Melanoma

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

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

Non-Small Cell Lung Cancer (NSCLC)

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

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

In patients with tumour EGFR or ALK genomic aberrations, Opdivo should be used after progression on or after targeted therapy.

Renal Cell Carcinoma (RCC)

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

Classical Hodgkin lymphoma (cHL)

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

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Opdivo as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum based therapy.

International regulatory status

At the time the TGA considered this application, a similar application had been approved or was under consideration in the countries or regions as shown in Table 1 and as described below.

Table 1: International regulatory status

Country/region	Submission date and status	Approved Indication
Canada	9 March 2017 Under review	
European Union (EU; via Centralised procedure)	25 August 2016 Approved 2 June 2017	Opdivo as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.
Switzerland	11 November 2016 Under review	
USA	2 September 2016 Approved 2 February 2017	Locally advanced or metastatic urothelial carcinoma who: have disease progression during or following platinum-containing chemotherapy have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

The product for a similar indication had also received approval in Peru, Argentina, Lebanon, Thailand, Korea, Hong Kong, Taiwan, and Saudi Arabia, and was under review in Israel, Russia, Brazil, Colombia, Venuzuela, Egypt and had been rejected in Turkey (due to a lack of a Phase III study).

Product Information

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

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2016-03898-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	31 January 2017
First round evaluation completed	30 June 2017
Sponsor provides responses on questions raised in first round evaluation	29 August 2017
Second round evaluation completed	26 September 2017
Delegate's Overall benefit-risk assessment	26 October 2017
Sponsor's pre-Advisory Committee response	13 November 2017
Advisory Committee meeting	Not applicable[1]
Registration decision (Outcome)	6 February 2018
Completion of administrative activities and registration on ARTG	9 February 2018
Number of working days from submission dossier acceptance to registration decision*	186 days

*Statutory timeframe for standard applications is 255 working days; 1) this submission was not referred to the Advisory Committee on Medicines (ACM).

A pre-submission teleconference was held between the TGA and the sponsor on 28 September 2016. At this teleconference, discussion took place relating to the appropriate historical control for nivolumab for the proposed extension of indication. The sponsor proposed taxanes (that is, paclitaxel or docetaxel), gemcitabine, pemetrexed and vinflunine as potential historical controls. The TGA requested the sponsor to undertake a review of the literature to justify the relevance of the historical control data in the dossier compared to the current standard of care in Australia. Subsequently, the sponsor sought the advice of Australian oncologists who treat patients with advanced or metastatic urothelial carcinoma. The oncologists advised the sponsor that in Australian clinical practice patients progressing following first-line platinum-containing chemotherapy would most likely receive a taxane (either paclitaxel or docetaxel). Therefore, the sponsor concluded that the choice of historical control presented in the regulatory dossier for the extension of indications is '*appropriate and relevant to Australian practice'.*

III. Quality findings

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

IV. Nonclinical findings

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

V. Clinical findings

Introduction

Urothelial carcinoma

Urothelial carcinoma (also known as urothelial cell carcinoma, transitional cell carcinoma of the urinary tract, or urothelial bladder cancer) is one of the most commonly occurring genitourinary malignancies. Urothelial carcinoma is the most common type of bladder cancer and accounts for 90% of cases.[2] Bladder cancer occurs more commonly in patients over the age of 60 than in younger patients and significantly more commonly in men than in women.

Bladder cancer is the ninth most common cancer in the world, with 429,793 new cases (330,380 in men and 99,413 in women) and 165,084 deaths due to the condition being reported in 2012.[3] In 2012, the global age standardised incidence rate for bladder cancer was estimated to be 6.1/100,000 persons and the age standardised mortality rate for the disease was estimated to be 1.4/100,000 persons.

In Australia (2014), bladder cancer (ICD-10/C67);[4] was estimated to be the eighth most commonly diagnosed cancer in men and the eighteenth most commonly diagnosed cancer in women.[5] The estimated incidence of bladder cancer in Australia in 2014 (based on 2002 to 2011 incidence data) was 2,060 males (age standardised rate (ASR) 16.7/100,000 persons) and 675 females (ASR 4.5/100,000 population). Death due to bladder cancer in Australia (2014) was estimated to be the twelfth most common cause of death due to cancer in males and the eighteenth most common cause in females. The estimated number of deaths due to bladder cancer in Australia in 2014 (based on 2002 to 2012 mortality data) was 780 males (ASR 6.5/100,000 population) and 335 females (ASR 2.1/100,000 population). The estimated relative survival rate for persons with bladder cancer using Australian data from 2007 to 2011 was approximately 53%.**Error! Bookmark not defined.**

Current treatment options

Australian guidelines

The sponsor states that there is no published literature describing the current Australian standard of care in patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy.

On 25 November 2016, the sponsor met with a group of Australian medical oncologists experienced in the treatment of patients with urothelial carcinoma in order to gauge the current Australian approach to treatment of these patients. The sponsor provided a copy of the minutes of this meeting signed by the independent chair. The outcomes of the meeting taken directly from the signed minutes are provided below.

[2] Jemal A, et al. Global cancer statistics. CA Cancer *J Clin*. 2011:61;69–90.
[3] Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013.
[4] ICD-10/C67: International Classification of Diseases, 10th edition; World Health Organization. C67 = Malignant neoplasm of the bladder.
[5] Australian Institute of Health and Welfare 2014. Cancer in Australia: an overview 2014. Cancer series No 90. Cat. no. CAN 88. Canberra: AIHW.

The advisors were asked to consider how they and their oncologist colleagues currently manage urothelial carcinoma in the second-line treatment setting. During ensuing discussion, the group agreed that:

1. In Australia, there are no national guidelines to guide clinicians' decision-making when managing urothelial carcinoma (that is, clinical practice is generally based on the available clinical trial data and guided by the prevailing reimbursement environment).
2. In Australia, there is no universally accepted 'standard of care' for patients whose urothelial carcinoma has progressed during/following first-line platinum-containing chemotherapy.

   The most commonly prescribed second-line treatment option would be a taxane (that is, either paclitaxel (in 70% of cases) or docetaxel (in 30% of cases)).
3. Vinflunine would be very rarely used in the second-line setting (if it is used at all), as this treatment is not currently available via the Pharmaceutical Benefits Scheme (PBS).

In Australia, neither paclitaxel nor docetaxel have been approved by the TGA for the treatment of urothelial carcinoma. Therefore, the use of these agents for the second-line treatment of patients with urothelial carcinoma after prior platinum therapy is considered to be 'off-label'. In Australia, vinflunine is the only TGA approved medicine for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen. The approved indication for vinflunine is consistent with the proposed extension of indication for nivolumab, and both medicines are considered to target the same patient group.

In the pivotal Phase III trial (Study VFL 302) supporting TGA approval of vinflunine, second-line treatment with vinflunine was compared to best supportive care (BSC) in patients with advanced transitional cell urothelial carcinoma previously treated with a first-line platinum-containing regimen.[6,7] The primary endpoint of median overall survival (OS) in all randomised patients was 6.9 months in the vinflunine arm (n = 253) compared to 4.6 months in the BSC arm (n = 117): hazard ratio (HR) = 0.88 (95% confidence interval (CI): 0.69, 1.12); p=0.2868, stratified log-rank test. The secondary endpoint of median progression-free survival (PFS) in the all randomised population was 3.0 months in the vinflunine arm (n = 253) and 1.5 months in the BSC arm (n = 117): HR = 0.68 (95% CI: 0.54, 0.86); p=0.0012 (log-rank test stratified). The secondary endpoint of objective response rate (ORR) (comprised of complete response (CR) + partial response (PR)) in evaluable patients in the vinflunine arm (n = 185) was 8.6% compared to 0% in the BSC arm (n = 85), with the difference in favour of vinflunine being statistically significant (difference = 8.6 (95% CI: 5.0, 13.7)).

It is noted that TGA approval of vinflunine was based on a confirmatory Phase III study with a controlled treatment arm (BSC). The current submission to extend the indications of nivolumab to include patients with urothelial carcinoma includes no confirmatory Phase III study comparing nivolumab with a controlled treatment arm. Based on the TGA approval for vinflunine it is considered that this medicine would be the most appropriate control treatment regimen for nivolumab in the proposed patient population. In the absence of a vinflunine control treatment arm, a control treatment arm consisting of placebo or best standard of care might be appropriate if supported by an acceptable justification.

[6] AUSPAR for Javlor vinflunine.
[7] Australian Product Information for Javlor vinflunine.

Global guidelines

The sponsor comments that there is no global standard of care for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy. The sponsor comments that for patients with metastatic urothelial carcinoma, standard first-line treatment involves platinum-based combination chemotherapy.[8,9] However, the sponsor notes that despite responses in 40% to 60% of patients with advanced urothelial carcinoma receiving first-line cisplatin-based chemotherapy, disease progression occurs in nearly all patients at a median of about 8 months.[10] In addition, 50% of patients are considered to be cisplatin ineligible due to poor performance status, impaired renal function, or comorbidity.[11] Therefore, these patients receive carboplatin regimens such as gemcitabine plus carboplatin, which is reported to offer a response rate of 41% and a median PFS of 5.8 months.[12]

The sponsor states that after platinum failure, the prognosis for patients with urothelial carcinoma is poor and commonly used second-line regimens yield only minimal efficacy (ORR of around 10%, median OS of 7 to 8 months).[13,14,15]

The most important risk factor identified in bladder cancer is smoking, with the presence of visceral or liver metastases, Eastern Cooperative Oncology Group (ECOG) performance scores greater than 0, and baseline haemoglobin lower than 10 g/dL predicting worse clinical outcomes for patients with advanced or metastatic disease after platinum failure. **Error! Bookmark not defined.**

The European Society for Medical Oncology (ESMO) Practice Guidelines for bladder cancer note that vinflunine is the only approved drug in Europe for the treatment of patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease.[7] The ESMO guidelines comment that it is unknown whether other agents used in this setting would have a similar benefit.

In the USA, vinflunine is not available for the treatment of urothelial carcinoma. However, atezolizumab, a programmed death-ligand 1 (PD-L1) blocking antibody, has been recently approved in the USA for the treatment of urothelial carcinoma under the US Food and Drug Administration's (FDA) accelerated approval procedures. In the USA, atezolizumab is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy;

[8] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Bladder cancer. Version 2. 2016.
[9] Bellmunt J et al. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014; 25: SuppL 3: iii 40-48.
[10] Von der Maase H et al. 2005. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Onc.* 2005; 23: 4602–4608.
[11] Sternberg C, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. *Lancet Oncol.* 2015; 16: 76-86.
[12] De Santis M, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol*. 2012; 30: 191-199.
[13] Ortmann C and Mazhar D. Second-line systemic therapy for metastatic urothelial carcinoma of the bladder. *Future Oncol.* 2013; 9: 1637–1651.
[14] Oing C, et al. Second Line Chemotherapy for Advanced and Metastatic Urothelial Carcinoma: Vinflunine and Beyond: A Comprehensive Review of the Current Literature. *J Urol.* 2016; 195: 254-263.
[15] Raggi D, et al. Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis. *Ann Oncol*. 2016; 27: 49–61.

- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.[16]

The response rate observed with atezolizumab for the treatment of patients with advanced urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy was 14.8% (95% CI: 11.1, 19.3) in the all treated population.**Error! Bookmark not defined.**,[17]

Data in the public domain from the US FDA website relating to the clinical review of atezolizumab for second-line treatment of advanced urothelial carcinoma indicates that there were no approved second-line therapies for this indication in the USA at the time of the atezolizumab submission. The review indicates that in the USA the standard of care for patients with advanced urothelial carcinoma is platinum-containing chemotherapy. However, almost all patients experience disease progression during or after platinum-containing chemotherapy and at the time of the atezolizumab US submission there were no effective or standard second-line therapies for these patients. The review noted that patients with progressive disease may have a limited survival time of 5 to 10 months. In addition, the review commented that off-label use of a few chemotherapeutics in this disease setting is associated with low response rates and short response durations along with considerable toxicities (for example, docetaxel, paclitaxel, and nab-paclitaxel or combination of paclitaxel with gemcitabine).

Clinical rationale

The sponsor's rationale for the submission is based on 'unmet medical need' for the treatment of patients with advanced or metastatic urothelial carcinoma in the platinum-refractory setting. The condition is serious with significant morbidity, mortality and limited treatment options.

While the sponsor's rationale is considered to be acceptable, vinflunine is approved in Australia for treatment of a patient population with urothelial carcinoma consistent with that for which the sponsor is seeking approval for nivolumab.

Contents of the clinical dossier

The dossier included a clinical trial program for the proposed extension of indication of nivolumab to include subjects with locally advanced unresectable or metastatic urothelial carcinoma whose disease has progressed or recurred during or following prior treatment with a platinum-containing agent.

The clinical dossier contained the following clinical data:

- Nivolumab population pharmacokinetic (PopPK) analysis in subjects with multiple tumour types. Report dated 5 August 2016.
- Study CA209275: a Phase II single-arm study of nivolumab monotherapy in subjects with metastatic or unresectable urothelial who have progressed or recurred following treatment with a platinum agent. Final clinical study report (CSR) dated 25 July 2016.
- Study CA209032: a Phase I/II open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumours. Interim CSR dated 29 June 2016.

[16] Tecentriq (atezolizumab) US Prescribing Information. Genentech, San Francisco, CA. May 2016.
[17] Rosenberg J, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 2016; 387: 1909-1920.

- Study CA209275: an ad hoc report on efficacy data based on a minimum of 9 month subject follow-up (that is, 3 months of additional follow-up from the database lock for the final CSR).
- Study CA209275: an ad hoc report on safety data based on a minimum of 9 month subject follow-up (that is, 3 months of additional follow-up from the database lock for the final CSR).
- A number of literature references.

In addition, the dossier contained:

An Introduction, Clinical Overview, Summary of Clinical Pharmacology Studies, Summary of Clinical Efficacy, Summary of Clinical Safety, Summary of Clinical Safety (Appendices), References (list only) and Synopses of Individual Studies.

Paediatric data

No paediatric data were provided in the submission. The sponsor indicated that it has not submitted paediatric data to the European Union (EU), but that it has an agreed Paediatric Investigation Plan (PIP) in Europe. The sponsor indicates that it is required to submit a report of a study conducted as part of the PIP in October 2017. The sponsor indicated that it has not submitted paediatric data to the FDA, but that it has an agreed Pediatric Plan under the relevant US legislation. The sponsor indicated that it has a waiver or deferral from having to submit a Paediatric Assessment in the USA. The sponsor indicated that its initial Pediatric Study Plan (PSP) to the FDA requested a full waiver of paediatric studies under the relevant legislation based on the finding that 'studies are impossible or highly impractical' since GPNMB-expressing, urinary bladder cancer does not occur in children. The FDA noted that urinary bladder cancer is included in the list of adult related conditions that may qualify the drug product for disease-specific waivers.

Good clinical practice

The submitted clinical studies were stated by the sponsor to have been conducted in accordance with Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

The submission included one population pharmacokinetic (PopPK) study (Study BMS-936558/MDX-1106) titled 'Nivolumab population pharmacokinetic analysis in subjects with multiple tumor types' and dated 5 August 2016.This study is reviewed below.

The sponsor states that it has previously submitted four PopPK analysis reports across different tumour types (melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC)). The pharmacokinetics (PK) of nivolumab in subjects with solid tumours and classical Hodgkin lymphoma (cHL) in these analyses was described by a stationary model in which nivolumab clearance (CL) was constant with respect to time. However, in a subsequent exploratory analysis following guidance from the US FDA, it was found that nivolumab CL tended to decrease with time. Therefore, the objectives of the new PopPK analysis (Study BMS-936558/MDX-1106) provided in this submission were to re-characterise the PopPK of nivolumab across multiple tumour types, including urothelial carcinoma, using a time-varying CL model. In addition, the PopPK analysis assessed the effects of a number of covariates on the PK of nivolumab.

Evaluator's conclusions on pharmacokinetics

The results for the PK parameters derived from the new PopPK analysis are consistent with the results from the previously reported PopPK analyses. Nivolumab was described by a linear two-compartment model with time-varying CL, such that CL decreased with time by approximately 26%. CL in subjects with urothelial carcinoma was similar to CL in subjects with NSCLC 2+ (that is, a 2% non-statistically significant increase). The effects of covariates on the PK of nivolumab were consistent with those previously described. Based on nivolumab CL and time-averaged steady state concentration ($C_{avg,ss}$) values, no dosage adjustment is needed in subjects with mild hepatic impairment or in subjects with mild or moderate renal impairment. Nivolumab exposures ($C_{avg,ss}$) were similar in Japanese (n=99) and non-Japanese subjects (n=2771) at 3 mg/kg Q2W (79.6 µg/mL and 86.9 µg/mL, respectively).

Pharmacodynamics

Studies providing pharmacodynamic data

The submission included immunogenicity data from the two new studies in subjects with urothelial carcinoma (Studies CA209275 and CA209032) and from an updated integrated analysis of subjects with various tumour types treated with nivolumab monotherapy. The immunogenicity results are summarised under *Safety* later in this section of the AusPAR.

Dosage selection for the pivotal study

The proposed dose of nivolumab monotherapy for the proposed usage in patients with urothelial carcinoma is 3 mg/kg every 2 weeks (Q2W). No other nivolumab dosage regimens are being proposed for the extension of indication to subjects with urothelial carcinoma.

The key efficacy and safety study was Study CA209275, a Phase II, open-label study of nivolumab monotherapy in subjects with metastatic or surgically unresectable urothelial carcinoma with disease progression or recurrence following treatment with a platinum agent. The sponsor states that the nivolumab monotherapy dose regimen of 3 mg/kg Q2W evaluated in this study was chosen because of a favourable risk-benefit ratio in multiple other tumour types in the large on-going Phase I Study CA209003 in subjects with various tumour types (colorectal cancer, melanoma, non-squamous cell NSCLC, squamous cell NSCLC, prostate cancer and RCC). The nivolumab 3 mg/kg Q2W dosage regimen was chosen based on the analyses of safety, efficacy, and exposure-response data from Study CA209003. Anti-tumour activity in Study CA209003 was observed at dose levels ranging from 1 to 10 mg/kg in melanoma, NSCLC and RCC, as well as at dose levels of 0.1 and 0.3 mg/kg in melanoma.

The observed anti-tumour activity in Study CA209003 in subjects with melanoma and NSCLC was highest at 3 mg/kg, suggesting that anti-tumour activity approaches a plateau at dose levels of 3 mg/kg and above. Consistent with these observations, the results of the exposure-response analyses for these tumour types in Study CA209003 showed that the probability of a tumour response tended to approach a plateau for trough concentrations produced by 3 mg/kg and 10 mg/kg Q2W. Furthermore, a favourable risk-benefit profile has been demonstrated with the 3 mg/kg dose in other ongoing trials, including the Phase III Study CA209037 in subjects with advanced melanoma.

Across the nivolumab program, doses up to 10 mg/kg have been adequately tolerated, and no maximum tolerated dose (MTD) has been identified. Based on the totality of the safety, efficacy, and exposure-response data from Studies CA209003 and CA209037, a dose of

3 mg/kg Q2W was selected as the dose anticipated to achieve an appropriate balance of efficacy and risk in subjects with urothelial carcinoma. Lastly, the dose and frequency of nivolumab in subjects with urothelial carcinoma in Study CA209275 has been aligned with the dosage regimen in the ongoing Study CA209032 in subjects with various tumour types (including advanced bladder cancer) submitted in the dossier along with Study CA209275.

Evaluator's conclusions on dosage selection for the pivotal study

The sponsor's rationale for the nivolumab monotherapy dose (3 mg/kg Q2W) selected for the key Phase II Study CA209275 is considered to be acceptable.

Efficacy

Studies providing efficacy data

The submission included two open-label studies providing evaluable efficacy data to support the application to register nivolumab monotherapy (3 mg/kg Q2W) for the treatment of patients with locally advanced unresectable or metastatic urothelial cancer after failure of prior platinum-containing therapy. The two studies were Study CA209275 (the key Phase II study) and Study CA209032 (supportive Phase I/II study). The two studies are outlined below in Table 3. Both studies have been fully evaluated.

Table 3: Outline of the two studies with evaluable efficacy data for patients with urothelial carcinoma

	Key Phase 2 Study – CA209275	Supportive Phase 1/2 Study – CA209032
Design	Phase 2, single-arm clinical trial of nivolumab in subjects with metastatic or unresectable UC whose disease had progressed or recurred following treatment with a platinum agent, or within 12-months of peri-operative (neoadjuvant or adjuvant) treatment with a platinum agent in the setting of cystectomy for localised muscle-invasive UC.	Phase 1/2, open-label, randomised, dose-ranging clinical trial of nivolumab combined with ipilimumab in subjects with advanced or solid metastatic solid tumours. The submission included supportive data for patients with UC treated with nivolumab monotherapy.
Treatment	Nivolumab 3 mg/kg Q2W; monotherapy	Nivolumab 3 mg/kg Q2W; monotherapy.
Primary efficacy endpoint	Confirmed ORR based on BIRC assessments (using RECIST 1.1) in subjects with tumour expressing PD-L1 (membranous staining in ≥ 5% and ≥ 1% tumour cells) and overall treated subjects.	Confirmed ORR based on investigator assessments (using RECIST 1.1)
Additional efficacy endpoints	DOR and PFS based on BIRC assessments; ORR and PFS based on investigator assessments; OS; association between baseline tumour PD-L1 expression and efficacy; HR-QoL using the EQ-5D and EORTC QLQ-C30.	DOR and PFS based on investigator assessments; OS; association between baseline tumour PD-L1 expression and efficacy; HR-QoL using the EQ-5D.
Subjects	N = 270 treated, 265 with minimum pre-specified follow-up of 6 months were used in the efficacy analysis.	N = 78 treated.
Status	A final CSR based on 30 May 2016 database lock for primary endpoint analysis was submitted. Updated efficacy and safety reports with an additional 3 months of data from the database lock for the primary endpoint analysis were also submitted. The study is ongoing.	An interim CSR based on 24 March 2016 database lock was submitted. The study is ongoing.

Notes: UC = urothelial cancer; Q2W = every 2 weeks; ORR = objective response rate; BIRC = blinded independent review; RECIST = response evaluation criteria in solid tumours; PD-L1 = programmed death ligand 1; DOR = duration of response; PFS = progression free survival; OS = overall survival; HR-QOL = health related quality of life; EORTC QLC-C30 = European organisation for research and treatment of cancer quality of life questionnaire 30 items; EQ-5D = European Quality of Life – 5 dimensions; N= number of subjects; CSR = clinical study report

Evaluator's conclusions on efficacy

The efficacy data for nivolumab 3 mg/kg Q2W for the proposed usage in patients with urothelial carcinoma are considered to be promising, based on the confirmed objective response rate (ORR) (blinded independent review committee (BIRC) assessed) using Response evaluation criteria in solid tumours (RECIST) version 1.1 criteria from the key Phase II Study CA209275 in 265 subjects and the confirmed ORR (investigator assessed) using RECIST 1.1 criteria from the supportive Phase I/II Study CA209032 in 78 subjects. In

both studies, the lower bound 95% CI for the ORR was greater than the historical control ORR of 10% reported in the published literature for second-line, single-agent chemotherapy for the treatment of advanced or metastatic urothelial carcinoma.

However, interpretation of the efficacy data based on the ORR is limited as both Studies CA209275 and CA209032 were open-label and single-arm. Therefore, comparison of the ORR from the two studies with an historical control ORR from published data should be interpreted cautiously due to both known and unknown biases arising from cross-study comparisons. It is considered that the promising ORR data should be confirmed by an appropriately designed Phase III, randomised, controlled study comparing nivolumab with control treatment (for example, placebo, best supportive care, or vinflunine) for the proposed usage in patients with urothelial carcinoma.

In both Study CA209275 and Study CA209032, progression-free survival (PFS) and overall survival (OS) were secondary efficacy endpoints. This is inconsistent with the relevant TGA adopted EU guidelines relating to the evaluation of cancer medicines. The relevant TGA adopted European Medicines Agency (EMA) guideline for the evaluation of cancer medicines state that OS or PFS/disease-free survival (DFS) should be a primary efficacy endpoint for confirmatory Phase III oncology trials.[18] It is considered that meaningful clinical interpretation of the nivolumab PFS and OS data is precluded in the absence of a study with a control arm. Comparison of PFS and OS outcomes with historical control data should be considered to be exploratory rather than confirmatory.

Safety

Studies providing safety data

Integrated assessment of safety data in subjects with urothelial carcinoma

The Summary of Clinical Safety (SCS) included an integrated assessment of the safety data for nivolumab 3 mg/kg Q2W monotherapy for the treatment of subjects with locally advanced or metastatic urothelial carcinoma whose disease had progressed or recurred during or following treatment with a platinum-containing agent. This assessment was undertaken in accordance with a pre-specified integrated statistical analysis plan (SAP) (BMS-936558).

The integrated safety assessment in subjects with urothelial carcinoma included data from the key open-label, single-arm, Phase II Study CA209275 of nivolumab monotherapy in 270 treated subjects; and the supportive open-label, single-arm, Phase I/II Study CA209032 in 78 treated subjects in the nivolumab monotherapy urothelial carcinoma cohort. The database locks for the final clinical study report for Study CA209275 and the interim clinical study report for Study CA209275 were 30 May 2016 and 24 March 2016, respectively.

The integrated safety assessment included 348 subjects with urothelial carcinoma and was referred to in the SCS as the *integrated urothelial carcinoma population*. Both Study CA209275 and Study CA209032 included subjects with urothelial carcinoma treated with a nivolumab 3 mg/kg Q2W monotherapy dosing regimen and used the same method for collection of safety data. The integrated urothelial carcinoma population was identified by the sponsor as the key population for assessment of the safety of nivolumab monotherapy in subjects with urothelial carcinoma.

[18] CHMP/EWP/205/95/Rev.4/Corr: Guideline on the evaluation of anticancer medicinal products in man; European Medicines Agency (EMA), Revision 4; December 2011.

In the clinical evaluation report for this submission, the approach to the evaluation of the safety of nivolumab monotherapy for the proposed usage in subjects with urothelial carcinoma has been to focus on the data presented in the integrated urothelial carcinoma population. It is considered that this approach is justified because both studies used the same dosing schedule, the study populations were comparable and the submission included a satisfactory pre-specified SAP for the integrated safety summary.

Safety presentations of adverse events (AE) serious adverse events (SAE), and AEs leading to discontinuation, and laboratory abnormalities for the integrated safety summary were based on all treated subjects using a safety window of 30 days after last dose. The 30 day safety window was intended to provide a clean characterisation of the safety experience of nivolumab monotherapy without influence of AEs associated with subsequent therapies.

Safety update report for study CA209275

The submission also included a safety update report (SUR) for Study CA209275 dated 21 November 2016, with a database lock of 2 September 2016. The SUR provided an additional 3 months of follow-up safety data from that presented in the final clinical study report. The methods used for analyses of safety data in the SUR were consistent with those used for the final clinical study report. AEs were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) version 19.0 for the SUR and the final clinical study report. AEs were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria for the final clinical study report for Study CA209275, the integrated urothelial carcinoma population in the SCS, and the SUR for Study CA209275.

The nivolumab monotherapy AE profile from Study CA209275 presented in the SUR was consistent with the corresponding AE profiles presented in the final CSR for Study CA209275 and in the SCS for the integrated urothelial carcinoma population. Relevant safety data from the SUR for Study CA209275 have been presented below.

Patient exposure

Integrated urothelial carcinoma population

In the *integrated urothelial carcinoma population*, the majority of subjects (80.2%) received ≥ 90% of the planned nivolumab dose intensity. The median number of nivolumab doses received was 7.0 (range: 1, 46). The median duration of therapy was 3.25 months, with 52.6%, 33.3%, 15.8%, and 5.2% of subjects being treated for more than 3, 6, 9, or 12 months, respectively. The exposure parameters are summarised below in Table 4.

Table 4: Exposure in all treated subjects in the integrated urothelial carcinoma population

	CA209032 N = 78	CA209275 N = 270	CA209032 + CA209275 N = 348
NUMBER OF DOSES RECEIVED			
MEAN (SD)	13.6 (12.24)	9.3 (7.15)	10.2 (8.72)
MEDIAN (MIN - MAX)	8.5 (1 - 46)	7.0 (1 - 30)	7.0 (1 - 46)
CUMULATIVE DOSE (MG/KG)			
MEAN (SD)	40.55 (36.241)	27.82 (21.310)	30.67 (25.918)
MEDIAN (MIN - MAX)	25.88 (3.0 - 138.1)	21.06 (3.0 - 89.0)	21.44 (3.0 - 138.1)
RELATIVE DOSE INTENSITY			
>= 110%	0	0	0
90% TO < 110%	68 (87.2)	211 (78.1)	279 (80.2)
70% TO < 90%	9 (11.5)	51 (18.9)	60 (17.2)
50% TO < 70%	1 (1.3)	5 (1.9)	6 (1.7)
< 50%	0	3 (1.1)	3 (0.9)
DURATION OF THERAPY (MONTHS)			
MIN, MAX (A)	0.0, 20.7+	0.0, 13.4+	0.0, 20.7+
MEDIAN (95% CI) (B)	3.47 (2.33, 5.09)	3.25 (2.33, 3.48)	3.25 (2.73, 3.48)
N OFF TRT/N TREATED (%)	60/78 (76.9)	204/270 (75.6)	264/348 (75.9)
OTHER STATISTICS			
MEAN	6.10	4.13	4.57
STANDARD DEVIATION	5.891	3.437	4.187
> 3 MONTHS (%)	42 (53.8)	141 (52.2)	183 (52.6)
> 6 MONTHS (%)	29 (37.2)	87 (32.2)	116 (33.3)
> 9 MONTHS (%)	23 (29.5)	32 (11.9)	55 (15.8)
> 12 MONTHS (%)	16 (20.5)	2 (0.7)	18 (5.2)

Source: SCS. A = Symbol + indicates censored value; B = median computed using Kaplan-Meier method.

Safety update report for study CA209275

Consistent with data in the final clinical study report, 78.1% of all treated subjects in Study CA209275 (SUR) received ≥ 90% of the planned dose intensity and the median number of nivolumab doses received was 7.0 (range: 1, 37). The median duration of therapy in the SUR remained at 3.25 months, with 52.2%, 32.2%, 23.7%, and 7.4% of subjects being treated for more than 3, 6, 9, or 12 months, respectively.

Safety issues with the potential for major regulatory impact

Overview

The risks of treatment with nivolumab monotherapy (3 mg/kg Q2W) in subjects with urothelial carcinoma are considered to be consistent with the known risks of treatment with nivolumab monotherapy for other tumour types for which the drug is approved. No new or unexpected risks associated with nivolumab monotherapy were identified in subjects with urothelial carcinoma.

Safety in special groups and situations

Intrinsic and extrinsic factors

In the *integrated urothelial carcinoma population*, the frequencies of all-causality and drug related AEs among all treated subjects for subgroups of gender, race, age, and region were consistent with the AE frequencies in the overall treated population. However, interpretation of the AE data based on differences in race is limited due to the marked imbalance in racial groups (that is, White = 87.1%, n=303; Asian = 8.9%, n=31; and Black or African American = 1.7%, n=6).

Small numerical differences in frequencies of AEs were observed based on gender. There were 265 male and 83 female treated subjects. Drug related AEs (any grade) and AEs (Grade 3 or 4) were reported more frequently in female subjects (72.3% and 25.3%, respectively) than in male subjects (67.5% and 17.0%, respectively). There were also small numerical differences of doubtful clinical significance based on region (Japan, USA, rest of world) in drug related AEs (any grade) and AEs (Grade 3 or 4).

Baseline PD-L1 expression

In Studies CA209275 and CA209032, no consistent differences were observed in the frequencies of AEs by PD-L1 cohorts.

Other special groups and situations

There was no new information relating to drug interactions, use in pregnancy and lactation, overdose, and drug abuse. No AEs related to nivolumab suggestive of withdrawal or rebound were reported during the clinical studies.

Nivolumab may have a detrimental effect on the ability to drive and operate machinery as treatment with the drug was associated with a high incidence of fatigue (any grade, all causality) in the integrated urothelial carcinoma population (37.1%, n = 129). Dizziness (any grade, all causality) was also reported in 1.1% (n = 4) of subjects in the integrated urothelial carcinoma population.

Immunogenicity

Study CA209275

Immunogenicity was an exploratory endpoint in Study CA209275. Immunogenicity data were available for 219 all treated subjects (that is, at Baseline and at least one post-baseline assessment). The results are summarised below:

- There were 11 (5.0%) subjects with an anti-drug antibody (ADA) positive sample at Baseline
- There were 52 (23.7%) subjects with at least one ADA positive sample relative to Baseline after initiation of treatment. Of these 52 subjects, no subjects were persistently positive, 24 (11.0%) subjects were not persistently positive but were positive at the last sample, and 28 (12.8%) subjects were not persistently positive but were negative at the last sample. Persistent positive subjects were required to have ADA positive samples at 2 or more consecutive time-points, with the first and last ADA positive samples being at least 16 weeks apart
- In all ADA positive subjects the ADA titres were low (range: 1 to 32)
- There were 4 (1.8%) subjects who were neutralising ADA positive (Nab positive). ADA titres were low (≤ 32) for these 4 subjects
- There were 167 ADA negative subjects.

Of the nivolumab treated subjects who were evaluable for ADA, 4 ADA negative subjects (2.4% (4/167)) experienced select AEs in the hypersensitivity/infusion reaction category, while hypersensitivity/infusion related reactions were not observed in any ADA positive subjects (0% (0/52)).

Of the 52 subjects who were ADA positive, 1 subject had a best overall response (BOR) of CR, 6 subjects had a BOR of PR, and 9 subjects had a BOR of stable disease (SD). Consequently, approximately 30% of ADA positive subjects had a response of CR or PR, or had SD. This response is consistent with the overall response observed in Study CA209275, which included both ADA positive and negative subjects.

Study CA209032

Immunogenicity was an exploratory endpoint in Study CA209032. Immunogenicity data were available for 69 all treated subjects with urothelial carcinoma (that is, at Baseline and at least one post-baseline assessment). The results are summarised below:

- There were 4 (5.8%) subjects with an ADA positive sample at Baseline
- There were 9 (13.0%) subjects with at least one ADA positive sample relative to Baseline after initiation of treatment. Of these 9 subjects, no subjects were

persistently positive, 1 (1.4%) subject was not persistently positive but was positive at the last sample, and 8 (11.6%) subjects were not persistently positive but negative at the last sample. Persistent positive subjects were required to have ADA positive samples at 2 or more consecutive time-points, with the first and last ADA positive samples being at least 16 weeks apart

- In all ADA positive subjects the ADA titres were low (range: 1 to 8)
- There was 1 (1.4%) Nab positive subject. This subject had only one Nab positive sample (Day 29) and the titre was low (8). All other ADA positive samples for this subject were Nab negative
- There were 60 (87.0%) ADA negative subjects.

Only 1 ADA positive subject (Nab negative) had Grade 1 hypersensitivity/infusion reaction on Day 1 after the first dose of nivolumab. This subject was ADA positive at Days 1, 15, 29, and 99 with titres of 2, 4, 8, and 2, respectively. The subject continued to receive nivolumab treatment for 6 months with no other occurrences of hypersensitivity/infusion reaction. The other 8 ADA positive subjects experienced no hypersensitivity/infusion reactions.

In the 9 ADA positive subjects, 1 had CR, 1 had PR, 4 had a SD, and 3 (including the Nab positive subject) had PD.

Integrated analysis

An integrated analysis of immunogenicity was provided in the Summary of Clinical Pharmacology. The pooled analysis of nivolumab ADA assessments was performed with data available from the following sponsor-sponsored studies in which ADA was assessed by the current sensitive and drug tolerant assay: Studies CA209037, CA209063, CA209066, CA209017, CA209057, CA209067 (nivolumab monotherapy arm), CA209025, CA209039, CA209205, CA209141, CA209032 (urothelial carcinoma subjects only), and CA209275. The pooled analysis included subjects with urothelial carcinoma from Studies CA209275 and CA209032.

Of 2022 subjects treated with nivolumab 3 mg/kg Q2W and evaluable for the presence of ADA, 231 (11.4%) subjects tested positive for ADA after the initiation of treatment. Of the 231 subjects who were ADA positive, only 2 (0.1%) were persistent ADA positive, and Nabs were detected in only 15 (0.7%). The impact of immunogenicity on nivolumab clearance was assessed in the PopPK analysis. ADA positivity was associated with a 14% increase in nivolumab CL, which was not considered to be clinically relevant. No association was established between the presence of ADA and hypersensitivity or infusion reactions, suggesting that ADA does not alter the safety profile of nivolumab.

Post marketing data

There were no post-marketing data for subjects with urothelial carcinoma treated with nivolumab monotherapy.

Evaluator's conclusions on safety

Safety data in 348 subjects with urothelial carcinoma treated with nivolumab monotherapy (3 mg/kg Q2W) were consistent with safety data in 2227 subjects with other tumour types treated with nivolumab monotherapy. No new safety signals associated with nivolumab monotherapy were identified in treated subjects with urothelial carcinoma.

Of the 348 subjects in the integrated urothelial carcinoma population treated with nivolumab 3 mg/kg Q2W, the majority of subjects (80.9%) received ≥ 90% of the planned

nivolumab dose intensity. The median number of nivolumab doses received was 7.0 (range: 1, 46). The median duration of treatment was 3.3 months (range: 0 to 20.7 [censored value] months), and 52.6%, 33.3%, 15.8%, and 5.2% of subjects were treated for more than 3, 6, 9, or 12 months, respectively. Most subjects (96.0%) received all doses of nivolumab without an infusion interruption (96.0%), infusion rate reduction (98.9%), or dose delay (61.2%).

The safety AE profile for Study CA209275 from the SUR included data from an additional 3 months of follow-up from the database lock for the final CSR for Study CA209275. The AE safety profiles from the SUR and the final CSR were consistent with each other. There were small numerical increases in some AE categories in the SUR compared with the final CSR. This is not unexpected due to the 3 months of additional follow-up for all subjects and treatment for some subjects in the SUR compared to the final CSR. However, no new safety signals for nivolumab monotherapy were observed in the SUR.

First round benefit-risk assessment

First round assessment of benefits

The benefits of nivolumab 3 mg/kg Q2W for the treatment of subjects with locally advanced or metastatic urothelial carcinoma whose disease has progressed or recurred during or following treatment with a platinum-containing agent are promising. However, interpretation of the benefits of treatment for the proposed usage in patients with urothelial carcinoma is limited due to the absence of confirmatory, controlled efficacy data. Both efficacy Studies CA209275 and CA209032 were open label and single-arm. Therefore, it is considered that the promising benefits shown in the two studies should be confirmed by efficacy data from an appropriately designed Phase III, randomised, controlled study.

In both studies, the lower bound 95% CI for the ORR (primary efficacy endpoint) was greater than the historical control ORR of 10% based on second-line, single-agent chemotherapy studies for the treatment of advanced or metastatic urothelial carcinoma. In the key Phase II Study CA209275, in the primary analysis the confirmed ORR (BIRC assessed) using RECIST 1.1 criteria was 19.6% (52/265) (95% CI: 15.0, 24.9), with 6 (2.3%) subjects reporting CR and 46 (17.4%) subjects reporting PR. In Study CA209275, the ORR in the final clinical study report (primary analysis) was consistent with the ORR in Addendum 01, which included data from an additional 3 months of follow-up. In the supportive Phase I/II Study CA209032, the confirmed ORR (investigator assessed) using RECIST 1.1 criteria was 24.4% (19/78) (95% CI: 15.3, 35.4), with 5 (6.4%) subjects reporting CR and 14 (17.9%) subjects reporting PR.

In both Studies CA209275 and CA209032, OS and PFS were secondary efficacy endpoints and the results for both of these endpoints were consistent for the two studies. However, in the absence of a randomised control arm it is difficult to draw clinically meaningful conclusions about the benefits of treatment with nivolumab monotherapy on OS and PFS in subjects with urothelial carcinoma.

In Study CA209275, with a median follow-up of 7.00 months the median OS was 8.74 months (95% CI: 6.05, NA), with the Kaplan-Meier estimated 6-month OS rate being 57.0%. In Addendum 01, median OS was consistent with the result for this parameter in the final clinical study report (primary analysis), while Kaplan-Meier estimated 6 month and 12 month OS rates were 56.5% and 41.0%, respectively. In Study CA209032, with median follow-up of 9.69 months the median OS was 9.72 months (95% CI: 7.26, 16.16), with the Kaplan-Meier estimated 12-month OS rate being 45.6%. The sponsor comments that OS results with nivolumab monotherapy compare favourably to historical control

with single-agent chemotherapies (median OS = 7 to 8 months). However, it is considered that comparisons of OS between single-arm studies such as Study CA209275 and CA209032 and historical controls should be considered to be exploratory rather than confirmatory.

In Study CA209275, median PFS (BIRC assessed) was 2.00 months (95% CI: 1.87, 2.63), with the Kaplan-Meier estimated 6 month PFS rate being 25.2%. In Addendum 01, median PFS was the same as in the primary analysis, while Kaplan-Meier estimated 6 month and 12 month PFS rates were 26.1% and 16.1%, respectively. In Study CA209032, median PFS (investigator assessed) was 2.78 months (95% CI: 1.45, 5.85), with the Kaplan-Meier estimated 12 month PFS rate being 20.8%.

In both Studies CA209275 and CA209032, PD-L1 expression was assessed retrospectively with subjects being enrolled regardless of PD-L1 expression status. The efficacy data from both studies suggest that the benefits of treatment with nivolumab monotherapy in subjects with urothelial carcinoma increase with PD-L1 expression. However, based on the ORR results (primary analysis) from the key Phase II Study CA209275 subjects with PD-L1 < 1% and subjects with PD-L1 ≥ 1% both benefited from treatment with nivolumab monotherapy (that is, ORR: 16.1% (95% CI: 10.5, 23.1) versus 23.8% (95% CI: 16.5, 32.3), respectively). In this study, the ORR in subjects with PD-L1 ≥ 5% was 28.4% (95% CI: 18.9, 39.5) and the ORR in subjects with PD-L1 < 5% was 15.8% (95% CI: 10.8, 21.8), which taken together with the results for subjects with PD-L1 < 1% and ≥ 1% suggest that benefits (ORR) increase with PD-L1 expression.

First round assessment of risks

The risks of treatment with nivolumab monotherapy (3 mg/kg Q2W) in subjects with urothelial carcinoma are considered to be consistent with the known risks of treatment with nivolumab monotherapy for other tumour types for which the drug is approved. No new or unexpected risks associated with nivolumab monotherapy were identified in subjects with urothelial carcinoma.

In the integrated urothelial carcinoma population (n=348), drug related AEs (any grade) were reported in 68.7% of subjects and drug related AEs (Grade 3 or 4) were reported in 19.0% of subjects. Drug related AEs (any grade) reported in ≥ 5% of subjects were fatigue (21.0%), pruritus (13.8%), diarrhoea (8.9%), nausea (8.3%), decreased appetite (7.8%), hypothyroidism (7.2%), rash (6.0%), anaemia (5.5%), asthenia (5.2%), and rash-maculopapular (5.2%). Drug related AEs (Grade 3 or 4) reported in ≥ 1% of subjects were lipase increased (2.3%), fatigue (2.0%), amylase increased (1.7%), diarrhoea (1.4%), asthenia (1.1%), dyspnoea (1.1%), and anaemia (1.1%).

In the integrated urothelial carcinoma population (n=348) there were 5 deaths (14.4%) occurring within 30 days of the last dose and reported to be related to treatment with nivolumab. The 5 deaths included two cases of pneumonitis and one case each of respiratory failure, circulatory collapse, and thrombocytopaenia.

In the integrated urothelial carcinoma population (n=348), drug related SAEs (any grade) were reported in 9.5% of subjects and drug related SAEs (Grade 3 or 4) were reported in 6.6% of subjects. Drug related SAEs (any grade) reported in at least 2 subjects were diarrhoea (n=5, 1.4%), pneumonitis (n=5, 1.4%), fatigue (n=3, 0.9%), colitis (n=2, 0.6%), nausea (n=2, 0.6%) and pemphigoid (n=2, 0.6%). Drug related SAEs (Grade 3 or 4) reported in at least 2 subjects were diarrhoea (n=4, 1.1%), fatigue (n=3, 0.9%), colitis (n=2, 0.6%), nausea (n=2, 0.6%), pneumonitis (n=2, 0.6%) and pemphigoid (n=2, 0.6%).

In the integrated urothelial carcinoma population (n=348), drug related AEs (any grade) leading to treatment discontinuation were reported in 4.3% of subjects. Drug related AEs (any grade) leading to treatment discontinuation were pneumonitis (1.4%), pemphigoid (0.6%), rash pruritic (0.3%), rash maculo-papular (0.3%), dyspnoea (0.3%), interstitial

lung disease (0.3%), abdominal pain (0.3%), diarrhoea (0.3%), thrombocytopenia (0.3%) and circulatory collapse (0.3%). In the integrated urothelial carcinoma population (n=348), most subjects (96.0%) received all doses of nivolumab without an infusion interruption (96.0%), infusion rate reduction (98.9%), or dose delay (61.2%). Overall, the results suggest that AEs generally required no treatment or were manageable by symptomatic treatment or dose delay rather than discontinuation of nivolumab.

In the integrated urothelial carcinoma population (n=348), data were presented for pre-specified select AEs of special clinical interest (endocrine, gastrointestinal, hepatic, pulmonary, renal, skin and hypersensitivity/infusion reaction). The majority of select AEs reported were Grade 1 or 2 in severity, and most were considered to be drug related. The majority of select AEs events were manageable, with resolution occurring either spontaneously or when immune-modulating medications (mostly systemic corticosteroids) were administered. Some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

In the integrated urothelial carcinoma population (n=348), the most frequently reported drug related select AEs (any grade) were skin (23.0%) followed by endocrine (12.9%), gastrointestinal (9.5%), hepatic (4.0%), pulmonary (3.7%), renal (2.9%), and hypersensitivity/infusion reaction (1.4%). Drug related select AEs (any grade) reported in ≥ 1% of subjects in descending order of frequency were pruritus (13.4%), diarrhoea (8.9%), hypothyroidism (7.2%), rash (6.0%), rash maculo-papular (5.2%), hyperthyroidism (4.0%), pneumonitis (3.4%), blood thyroid stimulating hormone (TSH) increased (3.2%), alanine aminotransferase increased (3.2%), aspartate aminotransferase increased (2.0%), blood TSH decreased (1.4%), blood creatinine increased (1.4%) and blood alkaline phosphatase increased (1.1%). There were no reports of toxic epidermal necrolysis or Stevens-Johnson syndrome.

Data on other events of special interest (OESI) were also presented in the submission. These events do no fulfil all criteria to qualify as select AEs of special clinical interest, but may differ from AEs caused by non-immunotherapies and may require immunosuppression as part of their management. Analyses of OESIs had extended follow-up (100 days from the last dose of nivolumab). The only OESI reported in the integrated urothelial carcinoma population was pancreatitis (Grade 3 or 4 OESI), which was considered not to be related to the study drug. This OESI did not result in treatment discontinuation nor was it treated with immune-modulating medicines. Apart from pancreatitis, no other events of special interest were reported (that is, myasthenic syndrome, demyelinating event, GuillainBarré syndrome, uveitis, encephalitis, myositis, myocarditis, and rhabdomyolysis).

In the integrated urothelial carcinoma population, worsening on-treatment to Grade 1 to 4 levels relative to baseline were observed very commonly (≥ 10%) and commonly (≥ 1% to < 10%) for all measured laboratory parameters (that is, haematology, liver function, creatinine, electrolytes, TSH, pancreatic tests (amylase, lipase) and glucose). On-treatment worsening was primarily to Grade 1 or 2 levels of severity. Laboratory parameters worsening to Grade 3-4 levels reported in ≥ 2% of subjects, in decreasing order of frequency, were observed for hyponatraemia (10.0%), decreased absolute lymphocyte count (9.7%), decreased haemoglobin (8.1%), increased alkaline phosphatase (4.8%), hyperglycaemia (3.5%), increased aspartate aminotransferase (3.0%), increased total bilirubin (2.7%) and decreased platelet count (2.1%).

In the integrated urothelial carcinoma population, TSH levels > upper limit of normal (ULN) were reported in 29.1% of subjects and TSH levels < lower limit of normal (LLN) were reported in 23.0% of subjects. In this population, drug related select AEs (any grade) of hyperthyroidism and hypothyroidism were reported in 4.0% and 7.2% of subjects, respectively.

In the integrated urothelial carcinoma population, increasing amylase and lipase levels were both reported. Amylase levels worsening from baseline to any grade and Grade 3 or 4 were reported in 18.2% and 5.7% of subjects, respectively. Lipase levels worsening from baseline to any grade and Grade 3 or 4 were reported in 20.9% and 7.1% of subjects, respectively. The notable increases in amylase and lipase levels were not associated with an increased risk of pancreatitis, with only one case of pancreatitis occurring more than 100 days after the last dose of nivolumab being reported in the integrated urothelial carcinoma population.

In a pooled analysis of all relevant sponsor studies (including the two studies in subjects with urothelial carcinoma), 2022 subjects were treated with nivolumab 3 mg/kg Q2W and were evaluable for the presence ADAs. Of these 2022 subjects, 231 (11.4%) were ADA positive including 2 (0.1%) who were persistently ADA positive and 15 (0.7%) who were Nab positive. The sponsor reports that the safety profiles of the 15 Nab positive subjects were no different from those observed in ADA negative subjects. There were no acute infusion reactions, hypersensitivity events, or new AEs observed in subjects with Nabs. Out of the 15 Nab positive subjects, only 1 subject had a subsequent Nab positive sample. Out of the other 14 Nab positive subjects, 6 had no additional samples, 5 had additional samples which were ADA negative, and 3 had additional samples that were ADA positive, but Nab negative.

The risk profile of nivolumab in special groups does not give rise to concern.

First round assessment of benefit-risk balance

The benefits of nivolumab 3 mg/kg Q2W for the proposed usage in subjects with urothelial carcinoma (based on two open label, single arm studies) are considered to be promising but require confirmation with efficacy data from an appropriately designed Phase III, randomised, controlled study in the population of interest. The risks of nivolumab monotherapy for the proposed usage in subjects with urothelial carcinoma are considered to be acceptable and are consistent with the risks of the drug in subjects with other tumour types. However, in the absence of confirmatory Phase III efficacy data satisfactorily establishing the benefits of treatment with nivolumab monotherapy for the proposed usage in patients with urothelial carcinoma it is considered that the benefit-risk balance of the drug for the proposed usage is unfavourable.

First round recommendation regarding authorisation

It is recommended that the application to register nivolumab 3 mg/kg Q2W for the treatment of locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy be rejected on the grounds of inadequate demonstration of efficacy for the proposed indication. The reasons for rejection are provided below.

The submission included no confirmatory Phase III studies establishing the efficacy of nivolumab monotherapy for the proposed usage in patients with urothelial carcinoma. In particular, there were no confirmatory data establishing that nivolumab monotherapy provides comparable OS or PFS benefits to those observed with vinflunine, a chemotherapeutic agent approved in Australia for the treatment of a similar urothelial carcinoma indication to that proposed for nivolumab. The TGA adopted EMA guideline relating to the evaluation of cancer medicines indicates that in determining the efficacy of single-agent experimental medicines in Phase III confirmatory studies the agent should be compared to the 'best available' comparator.[18] It is considered that there is no reason to deviate from the TGA adopted guideline in the current submission, given that there is an appropriate registered comparator (vinflunine) for the indication of interest.

Neither the key Phase II Study CA209275, nor the supportive Phase I/II Study CA209032 pre-specified either OS or PFS as a primary efficacy endpoint, with both endpoints in both studies being secondary efficacy endpoints. The relevant TGA adopted EMA guideline for the evaluation of cancer medicines state that OS or PFS/DFS should be a primary efficacy endpoint for confirmatory Phase III oncology trials.[18] It is considered that there is no reason to deviate from the TGA adopted guideline in the current submission, given that there is an appropriate registered comparator (vinflunine) for the indication of interest.

In both efficacy Studies CA209275 and CA209032, the median OS was comparable to OS in historical controls. However, it is considered that comparisons of OS between single-arm studies such as Studies CA209275 and CA209032 and historical controls should be considered to be exploratory rather than confirmatory due to the limitations of cross-study comparisons for this parameter. The sponsor comments that 'single-arm trials do not adequately characterize time-to-event endpoints such as survival, TTP, or PFS. Because of variability in the natural history of many forms of cancer, a randomized study is necessary to evaluate time-to-event endpoints'.

In both efficacy Studies CA209275 and CA209032, the ORR (primary efficacy endpoint) and associated lower bound 95% CI was greater than the historical control ORR of 10% based on published data from second-line, single-agent chemotherapy studies for the treatment of advanced or metastatic urothelial carcinoma. The sponsor selected the ORR as the primary endpoint for the key single-arm Study CA209275 specifically to meet FDA accelerated approval criteria for new agents, based on the fact that there was no standard available therapy in the USA at the time of the submission for patients with metastatic or unresectable urothelial carcinoma who have failed on or following prior platinum containing treatment.

The situation in the USA differs from that in Australia where vinflunine is approved for the treatment of urothelial carcinoma in a patient population similar to that for which treatment with nivolumab is being proposed. Furthermore, the TGA has no accelerated approval program to allow for earlier approval of medicines based on surrogate endpoints (for example, ORR) where continued approval may be contingent on verification and description of clinical benefits in confirmatory trials. In Australia, approval is based on the submission including 'stand-alone' (that is to say, unconditional) evidence of efficacy sufficient to establish satisfactory clinical benefits of the medicine for the proposed usage. Consequently, the sponsor's reason for selecting single-arm, non-confirmatory, Phase I/II and Phase II studies with ORR as the primary endpoint to support registration in Australia is considered to be not justified.

It is considered that the ORR comparison between nivolumab monotherapy and the historical control in the single-arm studies are supportive rather than confirmatory due to the biases associated with cross-study comparisons (for example, different study designs, different patient characteristics, and different lengths of exposure). In addition, the ORR is a surrogate measure of the clinical benefits of treatment, which should be demonstrated by satisfactory results for PFS and OS. Therefore, while the ORR results from the two single-arm studies are promising it is considered that they should be confirmed by an appropriately designed Phase III, randomised, controlled study, which also includes PFS and/or OS as primary and/or secondary efficacy endpoints consistent with the relevant TGA adopted guideline.[18]

Clinical questions and second round evaluation

Second round evaluation overview

The sponsor's post-first round response was dated 29 August 2017. The sponsor's response to the first round clinical questions and the evaluator's comments relating to the response are provided below. In addition to the sponsor's response to the clinical questions, the sponsor noted the first round recommendation to reject the application on the grounds of inadequate demonstration of efficacy for the proposed indication and provided a detailed response addressing the issues raised by the negative recommendation. The sponsor stated that it 'believes it is important that there is an opportunity to address the clinical evaluator's concerns at this stage of the application rather than addressing these with the TGA delegate at a later stage (pre-ACM response)'.

Sponsor's response to first round questions

Question 1 (Administrative)

Does the sponsor intend to apply for a waiver from the EMA relating to submission of paediatric studies for the proposed extension of indication to include urothelial carcinoma?

Sponsor's response

As stated in [the dossier], the sponsor has an agreed upon Paediatric Investigation Plan (PIP) in Europe and does not intend to apply for a waiver for the proposed indication. The PIP covers the condition of solid tumours, which enables the sponsor to pursue paediatric development in any adult solid tumour type regardless of whether or not it is covered by a class waiver (that is, even if the class waiver is revoked). The PIP does not currently identify a specific solid tumour indication, apart from melanoma, for further development, but does state that a solid tumour must be identified based on earlier signal detection studies, which could then form the basis of a confirmatory study.

Evaluator's comment

The sponsor's response is acceptable. Paediatric studies of nivolumab for the treatment of advanced urothelial carcinoma are not warranted, given that the incidence of this disease in this patient population is likely to be rare.

Question 2 (Administrative)

Please provide a copy of the protocol for the ongoing Phase III Study CA209274 in patients with high-risk invasive urothelial carcinoma.

Sponsor's response

A copy of the protocol for Study CA209274 was provided: Study CA209274 is also known as CheckMate 274 (CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 274).

Evaluator's comment

Study CA209274 is a Phase III, randomised, double-blind, multicentre clinical trial of adjuvant nivolumab versus placebo in adult male or female subjects who have undergone radical resection of invasive urothelial carcinoma originating in the bladder or upper urinary tract (renal pelvis or ureter) within 120 days prior to randomisation and are at high risk of recurrence. The co-primary objectives of the study are to compare disease free survival for nivolumab versus placebo in (1) subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) who are at high risk of recurrence after undergoing radical resection of invasive urothelial carcinoma, and (2) all randomised subjects. The key secondary objective is determination of overall survival in all

randomised subjects. The study plans to randomise a total of 640 patients (1:1) to the treatment arms. Treatment is planned to continue until toxicity, disease recurrence, or withdrawal of consent. The planned maximum treatment duration is 1 year. After discontinuation of study therapy, subjects will be followed for survival and those that have not had a non-urothelial tract recurrence will be followed for recurrence.

The patient population for Study CA209274 (nivolumab as adjunct therapy following resected invasive urothelial carcinoma) differs from that for the pivotal and supportive Studies CA209275 and CA209032 (respectively) in the current submission (that is, metastatic or surgically unresectable urothelial carcinoma). The results of Study CA209274 are considered to be not critical to the approval of the current application, but the study report should be provided to the TGA for evaluation when it becomes available.

Question 3 (Efficacy)

Nivolumab for the treatment of locally advanced or metastatic urothelial carcinoma in subjects who have progressed during or following platinum-containing chemotherapy was recently approved by the US FDA. The approved US prescribing information for nivolumab (February 2017) indicates that the approved dose for treatment of urothelial carcinoma is 240 mg Q2W. This dose differs from the dose of 3 mg/kg used in the key Phase II Study CA209275 on which accelerated approval in the US was based and the dose being proposed for approval in the current submission.

Please comment on the reasons given by the FDA to the sponsor for approval of a 240 mg Q2W dose rather than a 3 mg/kg Q2W dose.

Sponsor's response

On 13 September 2016, the FDA approved the nivolumab 240 mg every 2 weeks (Q2W) dose for melanoma, NSCLC, and renal cell carcinoma (RCC), based on a population pharmacokinetic (PopPK) analysis in metastatic melanoma, NSCLC and RCC subjects. This analysis predicted exposures following nivolumab 240 mg Q2W would be comparable to those following the nivolumab 3 mg/kg Q2W dosing regimen. Additionally, the potential impact of changing the nivolumab dose from 3 mg/kg Q2W to 240 mg Q2W on efficacy and safety in subjects with metastatic melanoma, NSCLC, and RCC was assessed using exposure-response models. The probability of objective response and the hazard of Grade 3+ drug related AEs were similar between these two regimens. Therefore, the FDA had already reviewed and approved the PopPK data for the 240 mg Q2W dose for melanoma, NSCLC and RCC when urothelial carcinoma was under evaluation.

During review of the urothelial carcinoma dossier, the FDA requested information to support use and approval of the 240 mg Q2W regimen in urothelial carcinoma patients. A similar PopPK approach was used to predict exposures following administration of nivolumab 240 mg Q2W and compare to those following administration of nivolumab 3 mg/kg Q2W. Overall, the similarities of exposures, efficacy, and safety between these two regimens supported the change and approval from 3 mg/kg Q2W to 240 mg Q2W in urothelial carcinoma patients.

In Australia, the sponsor submitted in June 2017 an application (submission PM-2017-02207-1-4) to register the following dosing changes in addition to the currently approved 3 mg/kg Q2W dose of nivolumab: flat dose of 240 mg Q2W; flat dose of 480 mg once every 4 weeks (Q4W); shorter infusion time to 30 minutes.

This application (submission PM-2017-02207-1-4) is relevant to all nivolumab indications, including approved indications, those under TGA review, and future planned indications. It is based upon data gathered in the course of the extensive nivolumab development program across multiple solid and haematological tumour types (melanoma, SQ NSCLC, non squamous cell (NSQ) NSCLC, RCC, squamous cell carcinoma of the head and

neck (SCCHN), urothelial carcinoma, and cHL) as well as robust clinical pharmacology and quantitative systems pharmacology analyses.

Evaluator's comment

The sponsor's response is satisfactory. The currently proposed dosage for patients with urothelial carcinoma is 3 mg/kg administered IV over 60 minutes every 2 weeks, with treatment being continued as long as clinical benefit is observed or until no longer tolerated by the patient (*Dosage and Administration* section of the PI).

Second round benefit-risk assessment

Second round assessment of benefits

In response to the first round recommendation to reject the application on the grounds of inadequate demonstration of efficacy for the proposed usage, the sponsor provided a detailed justification supporting its decision to base its regulatory submission on two single-arm Phase II Studies CA209275 and CA209032 assessing ORR as the primary efficacy endpoint. Following consideration of the sponsor's justification, and after review of the submitted data, it is concluded that it is more likely than not that nivolumab provides a meaningful clinical benefit relating to overall response rate and duration of response for the treatment of the proposed indication.

In both Studies CA209275 and CA209032, the lower bound 95% CI for the ORR (primary efficacy endpoint) was greater than the historical control ORR of 10% based on second-line, single-agent chemotherapy studies for the treatment of advanced or metastatic urothelial carcinoma. In the key Phase II Study CA209275, the primary analysis confirmed that the ORR (BIRC assessed) using RECIST 1.1 criteria was 19.6% (52/265) (95% CI: 15.0, 24.9), with 6 (2.3%) subjects reporting CR and 46 (17.4%) subjects reporting PR. The ORR in Addendum 01 to the final CSR for Study CA209275, which included data from an additional 3 months of follow-up, was consistent with the primary analysis (that is, 20.0% (54/270) (95% CI: 15.4, 25.3); CR = 3.0% (8/270), PR = 17.0% (46/270)). In the supportive Phase I/II Study CA209032, the confirmed ORR (investigator assessed) using RECIST 1.1 criteria was 24.4% (19/78) (95% CI: 15.3, 35.4), with 5 (6.4%) subjects reporting CR and 14 (17.9%) subjects reporting PR. The confirmed ORRs from both Studies CA209275 and CA209032 were consistent.

Data summarised in the vinflunine PI from the pivotal Phase III Study VFL 302 indicates that the ORR for vinflunine was notably lower than that for the primary analysis of ORR for nivolumab from Studies CA209275 and CA209032 (that is, 8.6% versus 19.6% versus 24.4%, respectively). In addition, the ORRs for nivolumab from Studies CA209275 and CA209032 were greater than the ORR of 11.4% (95% CI: 7.9, 15.8) for the investigator's choice chemotherapy group (vinflunine (n=87), docetaxel (n=84), paclitaxel (n=84)) from the recently published KEYNOTE-045 trial.[19] In the KEYNOTE-045 trial, the ORR in the pembrolizumab group was 21% (95% CI: 16.4, 26.5), which is comparable to the ORRs observed with nivolumab in Studies CA2090275 and CA209032. Based on a meta-analysis to estimate outcomes with chemotherapy in the salvage setting of urothelial carcinoma, the ORR for vinflunine based on 3 evaluable studies was 11.7% (95% CI: 6.2, 20.9) and for single-agent taxanes (paclitaxel or docetaxel) based on 5 evaluable studies was 10.5% (95% CI: 6.9, 15.8).[20] The ORRs observed for nivolumab in Studies CA209295 and

[19] Bellmunt J, et al. Pembrolizumab as Second- Line Therapy for Advanced Urothelial Carcinoma. *N Eng J Med* 2017; 376: 1015-1026.
[20] Raggi D, et al. Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis. *Ann Oncol*. 2016; 27: 49-61.

CA0209032 were greater than the ORRs for vinflunine and single-agent taxanes (paclitaxel or docetaxel) reported in the meta-analysis.

The median duration of response to nivolumab in Study CA209275 (Addendum 01) was 10.35 months (range: 1.9+, 12.0+ months). This result compares favourably with the median duration of response to chemotherapy (vinflunine, docetaxel or paclitaxel) of 4.3 months (range: 1.4+, 15.4+ months) in the KEYNOTE-045 trial.[19] The median duration of response had not been reached in the pembrolizumab group at the data cut-off in the KEYNOTE-045 trial. In Study CA209032, the median duration of response to nivolumab had not been reached at data cut-off, but most of the responders had achieved a response of at least 6 months.

In both Studies CA209275 and CA209032, OS and PFS were secondary efficacy endpoints and the results for both of these endpoints were consistent for the two studies. In the absence of a randomised control arm in the two studies it cannot be confirmed that treatment with nivolumab has a beneficial effect on OS and PFS in patients with urothelial carcinoma. However, limited support for a beneficial effect of nivolumab treatment in patients with urothelial carcinoma for these two time-to-event endpoints is provided by cross-study comparisons of nivolumab with other treatments for patients with urothelial carcinoma.

In Study CA209275 (Addendum 01), the median duration of OS in all treated patients was 8.57 months (95% CI: 6.05, 11.27), with 154 (57.0%) deaths being reported in 270 all treated patients. The estimated OS rate at 12 months in all treated patients was 41.0% (95% CI: 34.8, 47.1). In Study CA209032, the median OS was 9.72 months (95% CI: 7.26, 16.16), with the estimated 12 month OS rate being 45.6% (95% CI: 34.2, 56.3). The estimated median duration of OS in Studies CA209275 and CA209032 were favourable compared to the corresponding value for vinflunine in Study VFL 302 (that is, 8.57 versus 9.72 versus 6.9 months, respectively).

The OS results from Study CA209275 (Addendum 01) and Study CA209032 are comparable to the results from the KEYNOTE-045 trial for the chemotherapy group (vinflunine, docetaxel or paclitaxel). In the KEYNOTE-045 trial , the median OS was 7.4 months (95% CI: 6.1, 8.3) in the chemotherapy group and 10.3 months (95% CI: 8.0, 11.8) in the pembrolizumab group, with estimated 12 month survival rates being 30.7% (95% CI: 25.0, 36.7) and 43.9% (95% CI: 37.8, 49.9%), respectively.[19] Based on a meta-analysis to estimate outcomes with chemotherapy in the salvage setting of urothelial carcinoma, median OS for vinflunine based on 3 evaluable studies was 7.20 months (95% CI: 6.30, 8.10) and for single-agent taxanes (paclitaxel or docetaxel) was 7.35 months (95% CI: 6.16, 8.55) based on 4 evaluable studies.[20]

In Study CA209275 (Addendum 01), the median PFS (BIRC assessed) was 2.00 months (95% CI: 1.87, 2.63) in all treated patients, with the estimated 12-month PFS rate being 16.1% (95% CI: 11.7, 21.1). In study CA209032, the median PFS (investigator assessed) was 2.78 months (95% CI: 1.45, 5.85), and the estimated 12-month PFS rate was 20.8% (95% CI: 12.3, 30.9). The estimated median duration of PFS in Studies CA209275 and CA209032 were comparable to the corresponding value for vinflunine in Study VFL 302 (that is, 2.0 versus 2.8 versus 3.0 months, respectively).

The results for PFS from Study CA209275 (Addendum 01) and Study CA209032 are comparable to the results from the KEYNOTE-045 trial for the chemotherapy group (vinflunine, docetaxel or paclitaxel). In the KEYNOTE-045 trial, median PFS was 3.3 months (95% CI: 2.3, 3.5) in the chemotherapy group and 2.1 months (95% CI: 2.0, 3.5) in the pembrolizumab group, with estimated 12 month PFS rates being 6.2% (95% CI: 3.3, 10.2) and 16.8% (95% CI: 12.3, 22.0).[19] Based on a meta-analysis to estimate outcomes with chemotherapy in the salvage setting of urothelial carcinoma, median PFS for vinflunine based on 3 evaluable studies was 2.92 months (95% CI: 2.55, 3.29) and for

single-agent taxanes (paclitaxel or docetaxel) was 2.20 months (95% CI: 1.36, 3.04) based on 3 evaluable studies.[20]

In Studies CA209275 and CA209032, PD-L1 expression was assessed retrospectively with patients being enrolled regardless of PD-L1 expression status. The efficacy data from both studies suggest that the benefits of treatment with nivolumab in patients with urothelial carcinoma increase with PD-L1 expression. However, based on the ORR results (primary analysis) from the key Phase II Study CA209275 patients with PD-L1 < 1% and patients with PD-L1 ≥ 1% both benefited from treatment with nivolumab (that is, 16.1% (95% CI: 10.5, 23.1) vs 23.8% (95% CI: 16.5, 32.3), respectively). In this study, the ORR in patients with PD-L1 ≥ 5% was 28.4% (95% CI: 18.9, 39.5) and the ORR in patients with PD-L1 < 5% was 15.8% (95% CI: 10.8, 21.8), which taken together with the results for patients with PD-L1 < 1% and ≥ 1% suggest that benefits (ORR) increase with PD-L1 expression.

In Study CA209275, patient reported outcomes relating to quality of life was assessed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire 30-item score (QLQ-C30). Based on the QLQ-C30, during post-baseline follow-up through to treatment Week 49 the patients in the all treated group showed meaningful improvement in 5 scale scores (that is, mean change ≥ 10 points). These were dyspnoea (14.4 points), social functioning (11.7 points), global health status (11.7 points), appetite loss (12.2 points), and pain (11.1 points). Two scales that showed improvement in the primary analysis failed to show improvement in Addendum 01 following an additional 3 months of treatment (insomnia, financial difficulties).

In Study CA209275, patient reported outcomes relating to general health was assessed by the EuroQoL – 5 dimension questionnaire (EQ-5D)-3L. During post-baseline follow-up, the percentage of subjects reporting health problems decreased by 10% for all dimensions of the EQ-5D (that is, mobility at Week 9; self-care at Week 33; usual activities at Week 17; pain/discomfort at Week 9; and anxiety/depression at Week 17). The proportion of patients reporting no health problems continued to increase or remain stable through Week 49 of treatment for all dimensions. The mean baseline EQ-5D VAS score was 60.3 and mean scores were higher than baseline at Week 9 on treatment (that is, 67.5). By Week 41, the average EQ-5D VAS was 78.0 points, which is the norm for the US population (the country with the largest representation in the study).

Second round assessment of risks

After consideration of the responses to the clinical questions, the risks of nivolumab for the proposed usage are unchanged from those presented in the first round assessment of risks, (shown above).

Second round assessment of benefit-risk

Following consideration of the sponsor's response to the first round recommendation to reject the application on the grounds of inadequate demonstration of efficacy for the proposed indication and after review of the submitted data it is concluded that the benefit-risk balance for nivolumab, given the proposed usage, is favourable.

Based on the data from the two clinical studies in patients with advanced urothelial carcinoma (Studies CA209275 and CA209032), it is considered that nivolumab provides a clinical meaning benefit as regards overall response to treatment (complete response plus partial response) and duration of response. This conclusion is based on comparison of the nivolumab data with response data from historical controls.

There are no confirmatory data relating to benefits of treatment in the proposed patient population as regards the time-to-event points of OS or PFS. However, while the lack of a comparator in Studies CA209275 and CA209032 limits the assessment of OS and PFS,

indirect cross-study comparisons suggest that both parameters in nivolumab treated patients are comparable to vinflunine and single-agent taxanes (paclitaxel or docetaxel).

The risks of treatment with nivolumab monotherapy (3 mg/kg Q2W) in patients with urothelial carcinoma are considered to be consistent with the known risks of treatment with nivolumab monotherapy for other tumour types for which the drug is approved. No new or unexpected risks associated with nivolumab monotherapy have been identified in patients with urothelial carcinoma in the submitted clinical data.

Second round recommendation regarding authorisation

Approval of Opdivo nivolumab is recommended as monotherapy for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy. The approval of this indication is based on objective response rate and duration of response.

The second round recommendation to approve the application differs from the first round recommendation to reject the application based on inadequate demonstration of efficacy for the proposed usage. The reasons for the second round recommendation to approve the indication have been discussed above.

VI. Pharmacovigilance findings

The TGA granted a waiver from the requirement for a Risk Management Plan (RMP) for this application. It was proposed that the RMP for the currently approved indications should be used for this indication.

Risk management plan

Proposed wording for conditions of registration

The nivolumab EU-Risk Management Plan (EU-RMP), version 6.2, dated 27 January 2017, data lock point 26 May 2016) with Australian Specific Annex (version 8.0, dated 17 March 2017) included with submission PM-2016-00712-1-4 and PM-2016-01920-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

VII. Overall conclusion and risk/benefit assessment

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

Quality

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

Nonclinical

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

Clinical

Pivotal Study CA209275 (CheckMate-275 trial)

This was a Phase II single-arm trial with enrolment from March to October 2015 at 63 sites in 11 countries (USA, Japan, Australia, and in Europe).

This study was published; this publication is based on 6 months follow-up.[21] The data submitted by the sponsor and evaluated by the TGA included an additional 3 months follow-up.

Inclusion and exclusion criteria

Inclusion criteria

Participants (N = 270) were ≥ 18 years with:

- Metastatic or surgically unresectable urothelial carcinoma
- Progression or recurrence after treatment:
- At least 1 platinum-containing regimen
- Within 12 months of peri-operative (neoadjuvant or adjuvant) platinum-containing regimen for localised muscle-invasive urothelial carcinoma
- ECOG: 0, 1
- Serum creatinine < 1.5 x ULN or ≥ 30 mL/min.

Exclusion criteria

- Active brain metastases
- Autoimmune disease
- Systemic treatment with corticosteroids.

Treatment

Nivolumab: 3 mg/kg Q2W.

Comparator: Nil; single-arm study.

Endpoints

Primary: ORR on BIRC for PD-L1 positive (≥ 5%, ≥ 1%), and overall.

Secondary: PFS, OS, and investigator assessed ORR.

Baseline characteristics

Tumour cell PD-L1 membrane expression (≥ 1% or ≥ 5% tumour cell membrane staining) was assessed at a central laboratory (Dako PD-L1 immunohistochemical 28-8 pharmDx kit, Dako North America, Carpenteria, CA, USA).

PD-L1 expression was not an inclusion criterion.

Measurement of the primary endpoint (ORR, BIRC) by RESIST 1.1 was done at baseline, then every 8 weeks for 48 weeks, then every 12 weeks.

The final submitted CSR was dated October 2016; with a database lock of September 2016. This clinical study report provided efficacy with an additional 3 months of follow-up (minimum follow-up of 8.3 months) and included data from an additional 5 Japanese subjects since the time of the primary analysis.

[21] Sharma P et al. Lancet Oncol 2017; 18: 312–22.

Table 5: Study CA209275 (CheckMate-275 trial) Selected baseline characteristics

Age (years) Md (range)	66 (38, 90)
men	78%
ECOG 0 1	 54% 46%
Liver mets	28%
LN only	16%
Visceral mets	84%
Time since last platinum chemo < 3 months 3-6 months 6-12 months 12+ months	 59% 21% 15% 6%

Participant flow

Table 1: Study CA209275 (CheckMate-275 trial) participant flow

Treated patients	270 (100%)
Continuing on treatment	66 (24%)
Treatment ceased	204 (76%)
Reason for ceasing treatment Disease progression Toxicity AE unrelated to study medicine Withdrew/loss to FU/etc	 144 (53%) 14 (5%) 34 (13%) 12 (5%)

Among all treated subjects, median follow-up for OS (time between first dose and clinical cut-off date) was 11.5 months at the time of the data cut for this addendum (range: 8.3 to 15.7 months), about 3 months longer than the follow-up at the time of the primary analysis.

Results

Table 7: Study CA209275 (CheckMate-275 trial) results

Study CA209275 (CheckMate-275 trial)	
Participants	N = 270
ORR	N = 54 (20.0%) 95% CI (15.4%, 25.3%)
CR	N = 8 (3%)
PR	N = 46 (17%)
DoR	Median = 10.4 months, range(≥ 1.9, ≥ 12.0)
OS	Median = 8.6 months, 95% CI (6.1, 11.3)
Median time to response	1 to 2 months

Table 8: Study CA209275 (CheckMate-275 trial) Results stratified by PD-L1

	PD-L1 < 1% N = 146	PD-L1 > 1% N = 124
ORR	16%, 95% CI (10%, 23%)	25%, 95% CI (18%, 34%)
DoR	10.4 months, range (3.7, 12.0+)	NR, range (1.9+, 12.0+)
OS	5.9 months, 95% CI (4.4, 8.1)	11.6 months, 95% CI (9.1, NE)

Data from the Study CA209032 urothelial monotherapy cohort (CheckMate032 trial; n = 78) with minimum follow-up of 9 months were consistent with those from Study CA209275. (Various doses of nivolumab/ipilumab; various cancers: metastatic urothelial carcinoma, triple negative breast, gastric, pancreatic, small cell lung cancer (SCLC), ovarian.) The study population in Study CA209032 was comparable to that in Study CA209275, with a median age of 65.5 years and a majority of subjects that were white (92.3%) and male (69.2%). The investigator assessed ORR was 24.4% (95% CI: 15.3, 35.4), including 5 subjects with a CR. At a minimum follow up of 9 months, the median DOR was not reached, with most (68.4%) of the responders still continuing in response as of database lock for this analysis.

At a median follow-up of 9.69 months, the median OS was 9.72 months and the OS rates at 6 and 12 months were 69.2% and 45.6%, respectively.

Safety

Integrated safety data were presented for 348 patients from Study CA209275 (n = 270) and Study CA209032 (n = 78). No new risks, beyond those identified for nivolumab for other indications, were identified.

Three deaths were attributed to nivolumab: pneumonitis, respiratory failure, and cardiovascular failure.

Clinical evaluator's recommendation

The clinical evaluator recommended approval.

Risk management plan

Proposed wording for conditions of registration

The nivolumab EU-Risk Management Plan (EU-RMP), version 6.2, dated 27 January 2017, data lock point 26 May 2016) with Australian Specific Annex (version 8.0, dated 17 March 2017) included with submission PM-2016-00712-1-4 and PM-2016-01920-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Risk-benefit analysis

Delegate's considerations

- Patients with advanced or metastatic urothelial carcinoma and failure of previous platinum-containing therapy have a poor prognosis.
- For nivolumab: ORR=20%; median DoR = 10.4 months; median OS = 8.6 months.

- ORR of 20.0% for nivolumab; 95% CI (15.4%, 25.3%) is better than the pre-specified historical control ORR of 10%:
  - ORR for vinflunine from the pivotal study for marketing approval was 8.6%.[22]
  - A systematic review reported an ORR of 12% for vinflunine and of 11% for paclitaxel/docetaxel.[20]
  - ORR was 11% for the control arm (investigator choice: vinflunine, paclitaxel, docetaxel) in Study KN045 (intervention: pembrolizumab).
- Median DoR in pivotal Study CA209275 was 10.4 months (7.5, not reported). For single agent chemotherapy (vinflunine, paclitaxel, or docetaxel) in the control arm of Study KN045: median DoR = 4.3 months. In the registration trial of vinflunine, median DoR = 7.4 months.
- Experience in other cancers (SCCHN, NSCLC, melanoma) shows that similar or higher ORR than chemotherapy, combined with longer DoR, translate into improvements in OS and PFS.
- Patients with PD-L1< 1% had shorter median OS than those with PD-L1 ≥ 1% (6 months versus 12 months). However, this is similar to median OS with chemotherapy, and there were fewer toxicities.
- The safety profile of monotherapy with nivolumab has been well-characterised and no new safety concerns were identified in the metastatic urothelial carcinoma setting.
- The main uncertainty is the pivotal study for registration is single arm; data on OS are difficult to interpret without contemporaneous controls, who have similar baseline care during treatment with nivolumab and who receive similar post-progression treatment.

Summary of issues

Advanced or metastatic urothelial carcinoma is an incurable disease. Post-platinum (second line) patients have a poor prognosis. There is no established standard-of-care for these patients. There is a high unmet clinical need.

The pivotal study was Study CA209275/the CheckMate-275 trial: a single-arm trial, n = 270; median follow-up = 11.5 months.

The objective response rate (ORR) was 20.0% (95% CI: 15.4%, 25.3%). This was superior to the pre-specified historical control (10%) for chemotherapy (for example, vinflunine, paclitaxel, or docetaxel).

The median duration of response (DoR) was 10.4 months, compared with chemotherapy (historical controls) of 4 to 7 months.

The safety profile of monotherapy with nivolumab has been well-characterised and no new safety concerns were identified in the metastatic urothelial carcinoma setting.

Proposed action

The Delegate had no reason to say, at this time, that the extension of indications for Opdivo should not be approved for registration.

[22] Bellmunt J, et al., Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009; 27: 44-54

Request for ACM advice

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice. Advice was sought from an expert cancer advisory group.

Sponsor's response to delegate's overview

The sponsor welcomes the TGA Delegate's assessment that there are no reasons to say, at this time, that the application for extension of indications for Opdivo should not be approved for registration.

Nivolumab has demonstrated a substantial improvement in overall objective response (ORR) compared to available therapies, which is supported by duration of response (DOR), and an acceptable and manageable safety profile that is consistent with that established across other tumour types for which nivolumab is already indicated. The data submitted and evaluated by the TGA support the use of nivolumab in addressing the high unmet medical need in subjects with locally advanced or metastatic urothelial cancer (UC) following prior platinum-containing therapy.

In recognition of the data in the application, the sponsor has proposed, as reflected in the Delegate's Overview, an amendment to the indication statement to include a note regarding the type of data used to support approval as follows:

> *Opdivo, as monotherapy is indicated for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy. The approval of this indication is based on objective response rate and duration of response. See Clinical Trials.*

BMS can also confirm that Opdivo has been approved for the treatment of urothelial carcinoma in the US (2 February 2017) and EU (2 June 2017).

Introduction

In Australia it is estimated that in 2017 the incidence of bladder cancer will total a number of 2995 cases and an estimated 1172 deaths.[23] Based on estimated Australian cases for 2017, bladder cancer now represents the eighth most common cancer in men and the eighteenth most common cancer in women. Based on relative survival in 2009-2013, the 5-year relative survival rate in Australia was poor at 53.3%.[23] For patients with metastatic UC, standard first-line treatment involves platinum-based combination chemotherapy.[24] Despite responses in 40 to 60% of patients with advanced UC receiving first-line cisplatin-based chemotherapy, disease progression occurs in nearly all patients at a median of about 8 months.[25] The prognosis for advanced or metastatic UC in the platinum refractory setting is poor and there is a clear unmet medical need for treatments that improve clinical outcomes. There is no global standard of care, with commonly used second-line regimens (for example, taxanes and vinflunine) yielding a modest ORR of ~10%, and a median OS of 7 to 8 months.[26] [27] [28]

[23] Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101. Cat. no. CAN 100. Canberra: AIHW
[24] Galsky MD. Bladder cancer: advances in treatment and research. *Clin Adv Hematol Oncol.* 2010; 8: 234–236.
[25] Von der Maase H et al. 2005. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Onc*. 2005. 23: 4602–4608
[26] Ortmann CA and Mazhar D. Second-line systemic therapy for metastatic urothelial carcinoma of the bladder. *Future Oncol* 2013; 9:1637–1651
[27] Oing C, et al. Second Line Chemotherapy for Advanced and Metastatic Urothelial Carcinoma: Vinflunine and Beyond: A Comprehensive Review of the Current Literature. *J Urol* 2016; 195: 254-263
[28] Raggi D, et al. Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis. *Ann Oncol*. 2016; 27: 49-61.

For Australian patients with locally advanced, unresectable or metastatic UC who progressed on or following platinum-containing chemotherapy, a significant unmet medical need exists, with a high proportion of patients that do not respond to available treatment.

Efficacy

In Studies CA209275 and CA209032, nivolumab monotherapy demonstrated clinically meaningful ORR with the lower bound of 95% CI for ORR exceeding 10%, the historical ORR for second-line single-agent chemotherapies commonly used for patients with advanced or metastatic urothelial carcinoma. In Study CA209275, the BIRC)-assessed ORR was 19.6% (95% CI: 15.0, 24.9) in all treated subjects (6 subjects achieved a CR), with pre-specified minimum follow-up of 6 months. DOR per BIRC in all treated subjects ranged from 1.9+ to 9.6+ months, with median DOR not reached at the time of database lock (DBL 30 May 2016). The number of ongoing responses was 40/52 (76.9%). The median overall survival (OS) was 8.74 months (95% CI: 6/05, NA) with a 6-month OS rate of 57.0%. An updated efficacy analysis from Study CA209275 with additional patient follow-up which was included in the submission (2 September 2016 DBL), demonstrated continued clinically meaningful efficacy. Similar to the primary analysis, the ORR at 20.0% compared favourably to the single agent chemotherapy historical control rate. At a median follow-up 11.5 months, median DOR was 10.4 months and the number of ongoing responses was 34/54 (63.0%) in the all treated efficacy population. The median OS was 8.57 months (95% CI: 6.05, 11.27). Supportive data is provided by the UC monotherapy cohort of Study CA209032. The investigator assessed ORR was 24.4% (95% CI: 15.3, 35.4) and the median DOR was not reached with DOR ranging from 4.4 months to 16.6+ months. In Study CA209032, with a median follow-up of 9.69 months, the median OS was 9.72 months with a 6-month OS rate of 69.2%. In both Studies CA209275 and CA209032, ORR observed was clinically meaningful, regardless of baseline tumour PD-L1 expression status. The sponsor agrees with the clinical evaluator that 'Based on the data from the two clinical studies in patients with advanced UC (Studies CA209275 andCA209032), it is considered that nivolumab provides a clinical meaning (sic) benefit as regards overall response to treatment (complete response plus partial response) and duration of response. This conclusion is based on comparison of the nivolumab data with response data from historical controls'.

The clinical evaluator found that 'based on a meta-analysis to estimate outcomes with chemotherapy in the salvage setting of UC, the ORR for vinflunine based on 3 evaluable studies was 11.7% (95% CI: 6.2, 20.9) and for single-agent taxanes (paclitaxel or docetaxel) based on 5 evaluable studies was 10.5% (95% CI: 6.9, 15.8). The ORRs observed for nivolumab in Studies CA2090275 and CA0209032 were greater than the ORRs for vinflunine and single-agent taxanes (paclitaxel or docetaxel) reported in the meta-analysis.' The tabulation below also demonstrates the favourable comparison of nivolumab data to that of single agent chemotherapy for the clinically important endpoints of median duration of response and overall survival. The clinical evaluator summarised this as follows: 'In summary, there are a number of lines of consistent evidence arising from cross-study comparisons suggesting that nivolumab is a promising treatment for the proposed indication. These include an ORR that is superior to historical data for vinflunine and taxanes including single-agent paclitaxel or docetaxel, a duration of response which compares favourably to data from the KEYNOTE-045 trial for single-agent chemotherapy (vinflunine, paclitaxel or docetaxel) and taxane combinations, a similar estimated 12 month survival rate compared to data from the KEYNOTE-045 trial for single-agent chemotherapy (vinflunine, paclitaxel or docetaxel), and median OS and PFS durations that are comparable to those for vinflunine from a Phase III study (Study VFL 302) and two Phase II studies (Studies VFL 202 and CA 011).'

Table 9: Summary of Study CA209275 Efficacy results compared with historical controls

	Nivolumab[1]	Meta-analysis of three vinflunine trials[2]	Meta-analysis of five paclitaxel or docetaxel trials[2]	KN-045 comparator arm (vinflunine, paclitaxel or docetaxel)[3]
Confirmed objective response (%)	20.0	11.7	10.5	11.4
Median duration of response (months)	10.4	NA	NA	4.3
Overall survival				
Median (months)	8.6	7.2	7.4	7.4
Rate (%) at 12 months	41.0	NA	NA	30.7

[1] Addendum 01 CSR CA209275; [2] Raggi 2016; [3] Belmunt 2017; NA = not available

Based upon the currently available efficacy data for nivolumab, a reputed Australian expert in the field of urothelial cancer has also stated in their opinion of the data that 'nivolumab is active in metastatic urothelial cancer and leads to substantial and long-lasting response in an, as yet, undefined subgroup of patients who comprise 20 to 25% of the total population.'

Safety

The safety profile of nivolumab monotherapy at the recommended dose and schedule of 3 mg/kg Q2W observed in Studies CA209275 and CA209032 is consistent with the known safety profile of nivolumab across other tumour types. The TGA Delegate concluded that 'The safety profile of monotherapy with nivolumab has been well-characterised and no new safety concerns were identified in the mUC setting'. This is also supported by an Australian clinical expert who has commented that '(the external expert) have no special concerns regarding this toxicity profile in this population'. The safety profile of nivolumab was favourable when compared to that observed for the historical control vinflunine. Drug-related AEs were reported in a lower percentage of subjects in Study CA209275 (64.4% all grades; 17.8% Grade 3 to 4 events) than in a pooled safety analysis of vinflunine (93.3% all grades; 48.9% Grade 3 to 4). Myelosuppression, commonly reported with vinflunine and resulting in Grade 3 to 4 decreases in neutrophil and/or leukocyte counts in approximately half of all treated patients, was not a safety concern with nivolumab treatment.

TGA Delegate identified uncertainty

'The main uncertainty is the pivotal study for registration is single arm; data on OS are difficult to interpret without contemporaneous controls, who have similar baseline care during treatment with nivolumab and who receive similar post-progression treatment.' The intent to pursue registration in this refractory setting was made after the demonstration that the ORR and durability of responses in both studies (Studies CA209275 and CA209032) compared favourably to that of commonly used agents in this setting. In addition, the median OS and OS rates compared favourably to what has been described in the literature with available chemotherapy agents in the management of patients with UC. While a single arm study, CA209275 was a well conducted study, with robust statistical analysis, demonstrated consistency across endpoints in a patient population that reflected clinical practice, and the data replicated the clinically relevant effect observed in a smaller patient population studied in Study CA209032. The absence of a control arm in both Studies CA209275 and CA209032 is acknowledged as a limitation which makes it challenging to separate out the natural history of disease from treatment effect as measured by time to event endpoints (for example, progression-free survival (PFS) or OS). However, ORR, the primary endpoint of both studies, is generally regarded as

an effect attributable to drug, not natural history. Nevertheless, it is expected that the higher ORR with a very long median duration of response would translate to improved survival. Indeed, improvement in ORR and DOR over chemotherapy with nivolumab in other tumour types with longer follow up has also translated into improvement in OS (for example, SQ NSCLC, NSQ NSCLC, SCCHN, and RCC). From the most recent 2 October 2017 database lock which provides 13 months additional follow-up (minimum 21.3 months), there is now added evidence of the long term benefit of nivolumab in this patient population. The ORR remains similar at 20.4%, but the median DOR has increased to 17.74 months, and the OS rate at 2 years is 29.4% with a median OS of 8.57 months (95% CI: 6.05 to 11.27 months). While these data were not available with the initial application, they are summarised below.

Table 10: Summary of efficacy results from Study CA209275 by database lock

	30-May 2016	2-Sep-2016 DBL	2-Oct-2017 DBL
Minimum follow up (months)	6	8.3	21.3
Confirmed objective response (%)	19.6	20.0	20.4
Median duration of response (months)	-	10.35	17.74
Overall survival			
Median (months)	8.74	8.57	8.57
Rate (%) at 6 months	57.0	56.6	56.7
Rate (%) at 12 months	-	41.0	40.3
Rate (%) at 24 months	-	-	29.4

This most recent data from 2 October 2017 database lock confirm the benefit of nivolumab in producing durable responses that provide clinical benefit to patients with advanced UC. Finally, an externally developed and validated prognostic factor survival model (Sonpavde 2016);[29] showed that when controlling for differences in baseline prognostic factors, OS at 1 year is substantially greater in Study CA209275 with nivolumab than if a similar group of patients were treated with chemotherapy (41.9% (95% CI: 35.9 to 48.3%) versus 23.5% ((95% CI: 21.5 to 25.5%)) (Attachment 2; not included in this AusPAR).[30] The traditional drug development paradigm in oncology is evolving as there is increasing demand for reduced time to drug approval in patients with cancer with high unmet medical need. Single-arm studies enable accelerated patient access to new treatment options while still enabling a reliable assessment of clinical benefit. The clinical evaluator agreed that sponsors can justify the use of study designs and endpoints other than those specified in the TGA adopted EU anticancer medicinal products guideline. Accordingly, numerous approvals have been achieved on the basis of results obtained from single-arm trials demonstrating substantial and durable anti-tumour activity. This has also been recognised by TGA, both for PD-1 inhibitors but also for other new therapies in areas of high unmet medical need. Examples include TGA approvals for nivolumab for classical Hodgkin lymphoma (cHL), pembrolizumab for SCCHN, osimertinib for NSCLC, and alectinib for NSCLC. Thus, the regulatory arena has become more accepting of different trial designs for populations with life-threatening conditions with few treatment options. In recognising the limitations of the available data for nivolumab in a post-platinum treatment setting, the sponsor proposes to add a note to the indication statement as shown below:

[29] Sonpavde G, et al. Improved 5-factor prognostic classification of patients receiving salvage systemic therapy for advanced urothelial carcinoma. *J Urol* 2016; 195:277-282.
[30] Pond GR, et al. Nivolumab demonstrates benefit over nomogram-predicted 12-month survival as salvage therapy for metastatic urothelial carcinoma. Abstract submitted to the American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium to be held on February 8-10, 2018 in San Francisco, CA

Opdivo, as monotherapy is indicated for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy. The approval of this indication is based on objective response rate and duration of response. See Clinical Trials.

This statement together with the information provided in the Clinical Trials section of the Opdivo PI facilitates a more transparent understanding of the extent of available data evaluated for the indication and follows a similar TGA agreed approach as that of the recently approved indication for Opdivo in cHL (submission PM-2016-00712-1-4) which was also based on a single-arm study. The clinical evaluator agreed with the amended indication statement in the second round recommendation for authorisation.

Conclusion

The totality of the efficacy and safety data submitted with this application support the use of Opdivo monotherapy at a dose and schedule of 3 mg/kg Q2W for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma in adults after prior platinum containing therapy. Nivolumab demonstrated a substantial improvement in ORR in reference to available therapies, which is supported by DOR, and an acceptable and manageable safety profile that is consistent with that established across tumour types, addressing a significant unmet medical need. Indeed, a local clinical expert has concluded that 'Nivolumab offers a treatment that, due to its low toxicity profile, can potentially be offered to a wider group of patients' The approval of Opdivo in Australia for patients with advanced or metastatic urothelial carcinoma would mark the first immunotherapy agent to be available in this tumour type, providing a new mechanism of action for clinicians that translates into impactful clinical outcomes for patients over currently available chemotherapies.

Outcome

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

Urothelial Carcinoma

Opdivo, as monotherapy is indicated for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy. The approval of this indication is based on objective response rate and duration of response in a single arm study.

The full indications are now:

Melanoma

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

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

Non-Small Cell Lung Cancer (NSCLC)

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

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

In patients with tumour EGFR or ALK genomic aberrations, Opdivo should be used after progression on or after targeted therapy.

Renal Cell Carcinoma (RCC)

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

Classical Hodgkin lymphoma (cHL)

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

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Opdivo as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum based therapy.

Urothelial Carcinoma

Opdivo, as monotherapy is indicated for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy. The approval of this indication is based on objective response rate and duration of response in a single arm study

Specific conditions of registration applying to these goods

- The nivolumab EU-Risk Management Plan (EU-RMP), version 6.2, dated 27 January 2017, data lock point 26 May 2016) with Australian Specific Annex (version 8.0, dated 17 March 2017) included with submission PM-2016-00712-1-4 and PM-2016-01920-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

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

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