



Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Australian Public Assessment Report for Opdivo

Active ingredient: Nivolumab

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

June 2023

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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
BICR	Blinded independent central review
CMI	Consumer Medicines Information
$C_{\max, \text{Dose1}}$	Post-Dose 1 maximum concentration
$C_{\min, \text{D28}}$	Trough concentration at Day 28
CSR	Clinical Study Report
DFS	Disease free survival
DLP	Data lock point
HR	Hazard ratio
MIBC	Muscle invasive bladder cancer
MIUC	Muscle invasive urothelial carcinoma
OS	Overall survival
PD-L1	Programmed death-ligand 1
PI	Product Information
RMP	Risk management plan
TGA	Therapeutic Goods Administration
UC	Urothelial carcinoma
PSUR	Periodic safety update report
US FDA	United States Food and Drug Administration

Product submission

Submission details

<i>Type of submission:</i>	Extension of indication
<i>Product name:</i>	Opdivo
<i>Active ingredient:</i>	Nivolumab
<i>Decision:</i>	Approved
<i>Date of decision:</i>	14 July 2022
<i>Date of entry onto ARTG:</i>	Date of entry onto ARTG
<i>ARTG number:</i>	231867, 231868, 318057
▼ Black Triangle Scheme	No
<i>Sponsor's name and address:</i>	Bristol-Myers Squibb Australia Pty Ltd Level 2, 4 Nexus Court Mulgrave VIC 3170
<i>Dose form:</i>	Concentrated solution for infusion
<i>Strengths:</i>	40 in 4 mL (10 mg/1 mL) 100 mg in 10 mL (10 mg/1 mL) 240 mg in 24 mL (10 mg/1 mL)
<i>Container:</i>	Vial
<i>Pack size:</i>	Single vial packs
<i>Approved therapeutic use for the current submission:</i>	<i>Opdivo, as monotherapy, is indicated for the adjuvant treatment of patients with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC.</i>
<i>Route of administration:</i>	Intravenous infusion
<i>Dosage:</i>	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.

Adjuvant Treatment of Muscle Invasive Urothelial Carcinoma

The recommended dose is either:

- 240 mg every 2 weeks (30 minute intravenous infusion duration); or
- 480 mg every 4 weeks (30 minute intravenous infusion duration).

Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated to maximum duration of 12 months.

For further information regarding dosage, refer to the Product Information.

Pregnancy category:

D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Bristol-Myers Squibb Australia Pty Ltd (the sponsor) to register Opdivo (nivolumab) 40 in 4 mL (10 mg/mL), 100 mg in 10 mL (10 mg/mL), 240 mg in 24 mL (10 mg/mL) concentrated solution for infusion (vials) for the following proposed indication/extension of indications/change in dose regime:¹

Opdivo, as monotherapy, is indicated for the adjuvant treatment of patients with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC.

Urothelial carcinoma (UC) of the bladder is among the ten most common cancers in the world. Urothelial carcinoma originates in the urothelial cells (also called transitional cells) that line the bladder, ureter, and renal pelvis. The majority (90%) of urothelial carcinomas originate in the urinary bladder, 8% originate in the renal pelvis and the remaining 2% in the ureter and

¹ This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

urethra.² Upper tract urothelial carcinoma is less common, with an estimated annual incidence in developed countries of approximately two cases per 100,000 people.³

Although the majority of patients present with non-invasive disease, 15% to 25% of urothelial carcinomas either present with or eventually progress to muscle invasive or metastatic disease.⁴ Once invasive into the muscularis propria, urothelial carcinoma of the bladder, commonly referred to as muscle invasive bladder cancer (MIBC), is an aggressive disease that requires multimodal treatment, which includes radical surgery or radiation therapy with or without chemotherapy. Despite multimodal treatment, more than 50% of patients with MIBC will eventually develop metastases.⁵

Current treatment options

Radical cystectomy is the standard of care for patients with MIBC.^{6,7} That procedure involves complete removal of the bladder, surrounding tissues and regional lymph nodes is a potentially curative treatment for MIBC, however more than half of patients undergoing radical cystectomy will eventually relapse.⁷

Platinum based neoadjuvant therapy offers a clear benefit in MIBC and a potential benefit in muscle invasive upper tract urothelial carcinoma. The role of adjuvant therapy in this setting is less clear. Adjuvant cisplatin-based chemotherapy is recommended for patients who have not received neoadjuvant chemotherapy and are cisplatin eligible.⁸ However, due to the low level of evidence this did not become a widely used strategy.²

Adjuvant cisplatin-based chemotherapy in patients who received neoadjuvant chemotherapy is currently not recommended.

Pembrolizumab, atezolizumab and avelumab are checkpoint inhibitors approved for treatment of MIBC but none have an indication for adjuvant treatment of patients with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC. The following checkpoint inhibitor indications are relevant to patients with MIUC:

Pembrolizumab:

- Monotherapy treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing therapy and whose tumours express programmed death-ligand 1 (PD-L1) (Combined Positive Score \geq 10) as determined by a

² National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Bladder Cancer, Version 5. 2020.

³ Siegel, R.L., et al. Cancer Statistics, 2021. *Cancer J Clin*, 2021. 71: 7.

⁴ Burger, M., et al. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol*, 2013. 63: 234.

⁵ Stecca C, Abdeljalil O, Sridhar SS. Metastatic Urothelial Cancer: a rapidly changing treatment landscape. *Ther Adv Med Oncol*. 2021;13:175.

⁶ Gakis G, Black PC, Bochner BH, et al. Systematic review on the fate of the remnant urothelium after radical cystectomy. *Eur Urol*. 2017;71(4):545-557.

⁷ European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer AU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023.

Available at: <https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer>

⁸ Vale CL. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *European Urology* 2005; 48:189-201.

validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

- Monotherapy treatment of patients with locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy.
- Treatment of patients with Bacillus Calmette-Guerin unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma *in-situ* with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy (provisional approval).

Atezolizumab is approved for cisplatin ineligible patients with locally advanced or metastatic urothelial carcinoma whose tumours express PD-L1 (PD-L1 stained tumour-infiltrating immune cells covering 5% or more of the tumour area), as determined by a validated test, or who are ineligible for any other platinum-containing chemotherapy regardless of the level of tumour PD-L1 expression.^{9,10}

Avelumab is approved for first line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy.^{11,12}

Regulatory status

The product received initial registration on the [Australian Register of Therapeutic Goods \(ARTG\)](#) on January 2016.¹³ At the time that the submission described in this AusPAR to extend the indications of Opdivo (nivolumab) was considered, Opdivo was approved for the treatment of urothelial carcinoma with the following indication:

Urothelial Carcinoma (UC)

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.

It was also approved for:

Melanoma

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

Opdivo, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma.

⁹ Tecentriq atezolizumab (rch) 840 mg/14 mL, and 1200 mg/20 mL injection concentrated vial (ARTG R: 277120, 310681) was first registered in Australia on 27 July 2017.

¹⁰ No AusPAR exists for this extension of indications.

¹¹ Bavencio avelumab (rch) 200 mg/10 mL concentrated solution for intravenous infusion vial, (ARTG R: 282729) was first registered on 3 January 2018.

¹² The AusPAR for Bavencio avelumab (rch), Merck Serono Australia Pty Ltd, submission PM-2016-03575-1-4 is available online at: <https://www.tga.gov.au/resources/auspar/auspar-avelumab>

¹³ The AusPAR for Opdivo nivolumab Bristol-Myers Squibb Australia Pty Ltd PM-2014-03852-1-4 (initial registration, as a new biological entity) is available online at: <https://www.tga.gov.au/resources/auspar/auspar-nivolumab>

Opdivo, in combination with ipilimumab, is indicated for the treatment of patients with unresectable or metastatic melanoma. The approval of this indication is based on a pre-specified comparison to ipilimumab monotherapy. All analyses comparing nivolumab monotherapy with the nivolumab/ipilimumab combination are descriptive.

Non-Small Cell Lung Cancer (NSCLC)

Opdivo, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumour aberrations.

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.

Malignant Pleural Mesothelioma (MPM)

Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of patients with unresectable malignant pleural mesothelioma.

Renal Cell Carcinoma (RCC)

Opdivo, in combination with ipilimumab, is indicated for the treatment of patients with intermediate/poor-risk, previously untreated advanced renal cell carcinoma.

Opdivo, in combination with cabozantinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma.

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

Classical Hodgkin Lymphoma (cHL)

Opdivo, as monotherapy, is indicated for the treatment of 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 patients progressing on or after platinum based therapy.

Hepatocellular Carcinoma (HCC)

Opdivo, as monotherapy, is indicated for the treatment of patients with hepatocellular carcinoma after prior sorafenib therapy. This indication is approved based on objective response rate and duration of response in a single arm study. An improvement in survival or disease-related symptoms has not been established.

Oesophageal Squamous Cell Carcinoma (OSCC)

Opdivo, as monotherapy, is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine and platinum based chemotherapy.

Adjuvant Oesophageal Cancer (OC) or Gastro-Oesophageal Junction Cancer (GOJC)

Opdivo, as monotherapy, is indicated for the adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer in patients who have received neoadjuvant chemoradiotherapy.

Gastric Cancer (GC), Gastro-oesophageal Junction Cancer (GOJC), or Oesophageal Adenocarcinoma (OAC)

Opdivo, in combination with fluoropyrimidine- and platinum-based combination chemotherapy, is indicated for the first-line treatment of patients with HER2 negative advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma.

At the time the TGA considered this submission, similar submissions had been approved in the United States of America on 19 August 2021, Switzerland on 28 February 2022, in the European Union on 1 April 2022 and several other countries. It was under consideration by other countries, including Canada.

The following table summarises some of these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	3 March 2021	Approved on 19 August 2021	<i>Adjuvant treatment of patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.</i>
Switzerland	14 June 2021	Approved on 28 February 2022	<p><i>Opdivo is indicated for the adjuvant treatment of adult patients with muscle invasive urothelial carcinoma (MIUC) with PD-L1 expression ≥ 1 %, who are at high risk of recurrence based on pathologic evidence (see "Properties/Effects") after undergoing complete (R0) radical resection of MIUC and who</i></p> <ul style="list-style-type: none"> <i>• received neo-adjuvant cisplatin chemotherapy or</i> <i>• have not received neoadjuvant cisplatin chemotherapy and are not eligible for or refused adjuvant cisplatin</i>

Region	Submission date	Status	Approved indications
European Union	8 March 2021	Approved 1 April 2022	<i>Opdivo as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression \geq 1%, who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1).</i>

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 and [Consumer Medicines Information \(CMI\)](#), please refer to the TGA [PI/CMI search facility](#).

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the [standard prescription medicines registration process](#).

Table 2: Timeline for Submission PM-2021-02518-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	2 August 2021
First round evaluation completed	24 December 2021
Sponsor provides responses on questions raised in first round evaluation	28 February 2022
Second round evaluation completed	30 March 2022
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	6 April 2022
Sponsor's pre-Advisory Committee response	17 May 2022
Advisory Committee meeting	2 June 2022
Registration decision (Outcome)	14 July 2022
Completion of administrative activities and registration on the ARTG	18 July 2022
Number of working days from submission dossier acceptance to registration decision*	197

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Quality

Quality evaluation is not required for this submission as there are no proposed changes to the quality of the currently approved product in Australia. The quality of the currently approved product is suitable for the proposed changes in this submission. A full quality evaluation was conducted at the time this product received initial registration.¹³

Nonclinical

No new nonclinical data or further nonclinical evaluation were required for this submission. The TGA considers that previously submitted and evaluated data satisfactorily address nonclinical aspects of safety/efficacy relating to this submission.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- Study CA209274 (the CheckMate 274 trial), a pivotal efficacy and safety, Phase III randomised, double-blind, multicentre study of adjuvant nivolumab versus placebo in subjects with high-risk invasive urothelial carcinoma.

The study information was provided in four parts:

- Primary clinical study report
- Erratum to primary clinical study report
- Blinded independent central review report
- Interim overall survival report
- Exposure/response report, providing pharmacokinetic/pharmacodynamic and safety pharmacology data
- Population pharmacokinetic analysis report
- Literature references

The exposure response and population pharmacokinetic analyses were performed with data from Study CA209274 and from previously submitted studies.

Study CA209274 (the CheckMate 274 trial)

Pharmacology

Population pharmacokinetics

The population pharmacokinetic report was submitted to support the dose regimen of 240 mg once every two weeks or 480 mg once every four weeks for the new indication of adjuvant treatment for patients who have undergone radical resection of muscle invasive urothelial carcinoma (MIUC). The 240 mg once every two weeks regimen was used in the pivotal clinical Study CA209274 (the CheckMate 274 trial). This regimen was confirmed from the re-estimated population pharmacokinetics model incorporating the data from the pivotal study. The 480 mg once every four weeks regimen was based on modelling and simulations using the pharmacokinetic data from the pivotal study. These alternative dose regimens are consistent with the dose regimens approved for other monotherapy indications for nivolumab. The weight-based dose regimen of 3 mg/kg once every two weeks approved for adjuvant treatment of melanoma has not been proposed for adjuvant treatment of MIUC.

Pharmacodynamics

The effect of nivolumab exposure, shown via trough concentration at Day 28 ($C_{\min,D28}$), on disease free survival (DFS) was dependent on whether patients with adjuvant MIUC treatment received prior neo-adjuvant cisplatin. In patients who received nivolumab treatment, but did not receive prior neo-adjuvant cisplatin treatment, nivolumab exposures were not significantly associated with risk of disease recurrence or death. In patients who received nivolumab treatment and prior neo-adjuvant cisplatin treatment, higher nivolumab exposures ($C_{\min,D28}$) were associated with significantly lower risk of disease recurrence or death than in patients with lower nivolumab exposures (hazard ratio (HR) = 0.30 at the 95th percentile of nivolumab 55 $\mu\text{g}/\text{mL}$ and HR = 0.59 at the 5th percentile of nivolumab 24 $\mu\text{g}/\text{mL}$ in reference to placebo).

Higher post-Dose 1 maximum concentration ($C_{\max,Dose1}$) in serum was associated with a significantly higher incidence of Grade 2 or higher severity immune-mediated adverse events (HR = 1.35 (95% confidence intervals: 1.09, 1.66) at the 95th percentile of 145 $\mu\text{g}/\text{mL}$ compared with the median of 60 $\mu\text{g}/\text{mL}$) across the nivolumab dose range of 0.3 mg/kg to 10 mg/kg. The finding that Grade 2 or higher severity immune-mediated adverse events incidence is a more sensitive endpoint for the effect of nivolumab exposure on safety is consistent with the mechanism of action of nivolumab and previous analyses, as immune-mediated adverse events are more likely to be related to nivolumab exposure than other adverse reactions.

Efficacy

Study CA209274 (the CheckMate 274 trial), was a Phase III, randomised, double-blind, placebo-controlled study of adjuvant nivolumab in patients who were within 120 days of radical resection of urothelial carcinoma of the bladder or upper urinary tract (renal pelvis or ureter) at high risk of recurrence. This study was conducted in 170 sites in 30 countries including Australia. It commenced in March 2016 and the submission contained the primary clinical study report. The study is ongoing.

Design

The co-primary objectives were to compare the disease-free survival (DFS) for nivolumab versus placebo in patients with tumours expressing PD-L1 ($\geq 1\%$ membranous staining in tumour cells) and all randomised patients.

Secondary objectives were:

- To compare the overall survival for nivolumab versus placebo in patients with tumours expressing PD-L1 ($\geq 1\%$ membranous staining in tumour cells) and all-randomised patients.
- To evaluate non-urothelial tract recurrence free survival in each randomised treatment arm (nivolumab versus placebo) in patients all-randomised patients with tumours expressing PD-L1 ($\geq 1\%$ membranous staining in tumour cells) and all-randomised patients.
- To evaluate the disease-specific survival (DSS) for nivolumab and placebo in patients with tumours expressing PD-L1 ($\geq 1\%$ membranous staining in tumour cells) and all randomised patients.

Patients had undergone radical resection of muscle invasive urothelial carcinoma (MIUC) originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence. They were randomised 1:1 to nivolumab 240 mg or placebo by intravenous infusion once every two weeks, stratified by the following factors:

- PD-L1 expression level ($\geq 1\%$ versus $< 1\%$, or indeterminate).
- Receipt of neo-adjuvant cisplatin based chemotherapy for invasive urothelial carcinoma (yes versus no).
- Pathologic status of disease in lymph nodes (node positive (N+) versus N0 or NX with less than 10 nodes removed versus N0 with 10 or more nodes removed).¹⁴

High risk of recurrence was defined as either 1) ypT2-ypT4a or ypN+;¹⁵ for patients who received neoadjuvant cisplatin; or 2) pT3-pT4a or pN+;¹⁶ for patients who did not receive neoadjuvant cisplatin and who also either were ineligible for or refused adjuvant cisplatin. Patients were stratified by pathologic nodal status (node positive (N+) versus N0 or NX with less than 10 nodes removed versus N0 with 10 or more nodes removed), tumour cells expressing PD-L1 ($\geq 1\%$ versus $< 1\%$ or indeterminate as determined by the central lab using the PD-L1 IHC 28-8 pharmDx assay), and use of neoadjuvant cisplatin (yes versus no).

¹⁴ In urothelial carcinoma, the following coding is used to describe regional lymph node involvement:

N+ denotes node positivity.

NX: The regional lymph nodes cannot be evaluated.

N0: The cancer has not spread to the regional lymph nodes.

N1: The cancer has spread to 1 regional lymph node in the pelvis.

N2: The cancer has spread to 2 or more regional lymph nodes in the pelvis.

N3: The cancer has spread to the common iliac lymph nodes, which are located behind the major arteries in the pelvis, above the bladder.

¹⁵ ypT2 denotes preoperative radiotherapy or chemotherapy (y) in a primary (p) tumour of T2 stage (or primary tumour invading muscularis propria).

ypT3 denotes preoperative radiotherapy or chemotherapy (y) in a primary (p) tumour of T3 stage (or primary tumour invading perivesical tissue).

ypT4 denotes preoperative radiotherapy or chemotherapy (y) in a primary (p) tumour of T4 stage (or primary tumour invading prostratic stroma, seminal vesicles, uterus or vagina (T4a) or directly invading pelvic wall or abdominal wall (T4b)).

ypN+ denotes preoperative radiotherapy or chemotherapy (y) in a primary (p) tumour with node positivity (or presence of cancer in regional lymph nodes).

¹⁶ pT3, pT4a and pN+ denote the same as above, but without preoperative radiotherapy or chemotherapy (y).

Treatment was to continue until recurrence or until unacceptable toxicity for a maximum treatment duration of one year.

The primary efficacy endpoint was disease free survival, assessed by the investigator for nivolumab versus placebo. This was evaluated in two populations: all-randomised patients and all-randomised patients with tumour cell PD-L1 expression level $\geq 1\%$. Disease free survival was programmatically determined based on the disease recurrence date provided by the investigator and was defined as the time between the date of randomisation and the date of the first documented recurrence (local urothelial tract, local non-urothelial tract or distant), or death (from any cause), whichever occurred first. Disease recurrence of the local urothelial tract was defined as any high and intermediate risk of non-muscle invasive bladder cancer (NMIBC) and any new invasive urothelial carcinoma in the lower or upper urothelial tract (defined as T2 or greater), including lesions thought to be a second primary urothelial carcinoma.

Disease free survival was calculated using two definitions. The primary definition of DFS accounted for subsequent anticancer therapy and new non-urothelial carcinoma primary cancer by censoring at the last evaluable disease assessment on or prior to the date of subsequent therapy/new non-urothelial carcinoma primary cancer and was used for this analysis.

- A subject with presence of disease at baseline was considered as having a DFS event on the randomisation date.
- A subject with no baseline disease assessment or no on-study disease assessment and no death was censored on the randomisation date.
- A subject who died without reported recurrence and no new anticancer therapy started nor new non-urothelial carcinoma primary cancer was considered to have disease recurrence on the date of death.
- For patients who remained alive and whose disease had not recurred, and no new anticancer therapy started nor new non-urothelial carcinoma primary cancer, DFS was censored on the date of last evaluable disease assessment.
- For patients who received new anticancer therapy without recurrence reported prior to or on the same day, DFS was censored at the date of last evaluable disease assessment prior to or on the date of initiation of subsequent therapy.
- For patients who had new non-urothelial carcinoma primary cancer without urothelial carcinoma recurrence reported prior to or on the same day, DFS was censored on the day of last evaluable disease assessment prior to or on the same date of diagnosis of new non-urothelial carcinoma primary cancer.

The secondary definition of DFS accounted for disease assessments occurring on or after initiation of subsequent anticancer therapy. The censoring scheme was the same as for the primary DFS definition except that new anticancer therapy censoring was ignored in this sensitivity analysis. The secondary definition of DFS accounted for new non-urothelial carcinoma primary cancer by censoring at the last evaluable disease assessment on or prior to the date of new non-urothelial carcinoma primary cancer.

The US FDA requested a blinded independent central review (BICR) for a random subset of 50% of all randomised patients. This BICR was set up retrospectively with an imaging vendor and the US FDA provided the 50% random subset. The BICR-assessed DFS used a last-patient-last-visit of 17 July 2020, and only scans and procedures that were in the database on that date were included in the analysis. The database lock occurred on 11 June 2021.

Results

A total of 709 patients were randomised and 699 were treated, of these 282 (40.3%) had tumours with PD-L1 \geq 1%. The median age was 67.0 years (range: 30 to 92 years), patients had a baseline Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 (62.8%), 1 (34.8%), or 2 (2.3%).¹⁷ The majority of patients were White (75.6%) and male (76.2%). The predominant tumour type was urinary bladder (79.0% of patients).

At study entry, 17.9%, 57.8%, and 16.8% of all randomised patients had Stage pT2, Stage pT3, and Stage pT4A disease (tumour stage)^{14,15,16} at the time of resection, respectively and 59.1% and 39.5% of patients had tumour cell PD-L1 expression $<$ 1% and \geq 1%, respectively and 0.3% of the patients were indeterminate.

Stratification factors based on information at Baseline were:

- tumour cell PD-L1 expression status at Baseline (\geq 1% (39.8% of patients) versus $<$ 1% (60.2% of patients));
- receipt of neo-adjuvant cisplatin based chemotherapy for MIUC (Yes (42.9% of patients) of patients]/No (57.1% of patients)); and
- pathologic status of disease in lymph nodes (N+ (42.5% of patients), N0 or NX with less than 10 nodes removed (31.6% of patients), N0 with 10 or more nodes removed (26.0% of patients)).

The primary clinical study report was created when it was estimated that approximately 85% of the planned DFS events would have occurred. During the evaluation an additional analysis became available which provided approximately five months of additional efficacy data. As of the 27 August 2020 database lock, (primary analysis) the median follow-up time was 20.90 months and 19.48 months for all randomised patients in the nivolumab and placebo arms, respectively. In all randomised patients with tumour cell PD-L1 expression \geq 1%, the median follow-up was 22.11 months for the nivolumab arm and 18.69 months for the placebo arm.

The primary efficacy results stratified by PD-L1 status are shown below and show superiority of nivolumab over placebo for DFS using either definition for all randomised patients and for patients with tumour PD-L1 expression \geq 1%.

¹⁷ **Eastern Cooperative Oncology Group (ECOG) Performance Status:** The ECOG has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work

2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 - Dead

Table 3: Study CA209274 (the CheckMate 274 trial) Disease free survival (all randomised and all randomised PD-L1 ≥ 1%)

Efficacy Parameter	All Randomised		All Randomised PD-L1 ≥1%	
	Placebo (N=356)	Nivolumab (N=353)	Placebo (N=142)	Nivolumab (N=140)
PRIMARY ENDPOINTS				
DFS Primary Definition				
Events,n(%)	204 (57.3)	170 (48.2)	81 (57.0)	55 (39.3)
Median DFS	10.84	20.76	8.41	NA
(95% CI), m ^a	(8.25, 13.86)	(16.49, 27.63)	(5.59, 21.19)	(21.19, NA)
HR ^b	0.70		0.55	
(% CI)	(98.22% CI: 0.55, 0.90)		(98.72% CI: 0.35, 0.85)	
Stratified log-rank p-value ^c	0.0008 ^d		0.0005 ^e	
Rate at 6 months	60.3	74.9	55.7	74.5
(95% CI), % ^a	(54.9, 65.3)	(69.9, 79.2)	(46.8, 63.6)	(66.2, 81.1)
DFS Secondary Definition				
Events,n(%)	205 (57.6)	170 (48.2)	81 (57.0)	55 (39.3)
Median DFS	10.84	20.80	8.41	NA
(95% CI), m ^a	(8.25, 13.86)	(17.05, 27.63)	(5.59, 21.19)	(22.01, NA)
HR ^b	0.70		0.54	
(% CI)	(98.22% CI: 0.55, 0.90)		(98.72% CI: 0.35, 0.84)	
Stratified log-rank p-value ^c	0.0006 ^d		0.0005 ^e	
Rate at 6 months	60.3	75.0	55.7	74.6
(95% CI), % ^a	(54.9, 65.3)	(70.0, 79.2)	(46.8, 63.6)	(66.4, 81.2)

As of the 27-Aug-2020 DBL, the median follow-up time was 20.90 months and 19.48 months for all randomised subjects in the nivolumab and placebo arms, respectively. In all randomised subjects with tumour cell PD-L1 expression ≥1%, the median follow-up was 22.11 months for the nivolumab arm and 18.69 months for the placebo arm.

a Based on Kaplan-Meier Estimates

b Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab over Placebo

c 2 sided p values from stratified regular log-rank test

d Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, PD-L1 status (≥1% versus <1%/indeterminate) as entered in the IRT

e Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in the IRT

Note: The primary definition of DFS accounted for subsequent anticancer therapy and new non-urothelial carcinoma primary cancer. The secondary definition of DFS accounted for disease assessments occurring on or after initiation of subsequent anticancer therapy.

CI = confidence interval, DBL = database lock, DFS = disease-free survival, HR = hazard ratio, m = months,

Source: Study CA209274 CSR Erratum Table 4.6-1.

Exploratory sensitivity analyses of DFS by various subgroups were conducted. Of note is the lack of any trend towards benefit of nivolumab for patients with tumours above the bladder (kidney pelvis and ureter). These patients comprised of approximately 20% of the study population. There was a small trend towards DFS favouring placebo for these patients, though this analysis was exploratory and the differences were not statistically significant. Exploratory sensitivity analyses also identified the subgroup of patients with tumour PD-L1 expression < 1% as having a trend towards higher median DFS rate in the nivolumab treatment group (HR 0.82; 95% CI 0.63 – 1.06), suggesting that nivolumab is effective as adjuvant therapy in this subgroup, though with less efficacy than in patients with tumour PD-L1 ≥ 1%. This group comprised the majority of patients in the study.

At the time of the 1 February 2021 cut-off date overall survival data were not mature (57.4% of the planned 404 overall survival events were observed for all randomised subjects and 84 (50.6%) of the planned 166 overall survival events were observed for all randomised subjects with tumour cell PD-L1 expression level ≥ 1%) and did not meet the pre-specified boundary for declaring the statistical significance.

Additional requested analyses

Due to concern that efficacy was predominantly accruing to patients with tumours expressing PD-L1 $\geq 1\%$ the exploratory subgroup analysis of patients with PD-L1 $< 1\%$ was requested. The following was provided by the sponsor, with a longer duration of assessment than the primary analysis. A benefit in DFS was seen in the PD-L1 $< 1\%$ patient population with a HR of 0.80 (95% CI: 0.62, 1.03), and median DFS of 17.68 months (95% CI: 14.06, 22.37) for nivolumab versus 11.07 months (95% CI: 8.31, 16.89) for placebo.

Table 4: Study CA209274 (the CheckMate 274 trial) Primary and secondary efficacy endpoints for all-randomised subjects with tumour cell PD-L1 $< 1\%$ (from 19 May 2021 database lock with data cut-off date of 1 February 2021)

Efficacy Parameter	Placebo (N = 207)	Nivolumab (N = 207)
PRIMARY ENDPOINTS		
DFS Primary Definition		
Events, n (%)	124 (59.9)	114 (55.1)
Median DFS (95% CI) ^a , months	11.07 (8.31, 16.89)	17.68 (14.06, 22.37)
HR (95% CI) ^b	0.80 (0.62, 1.03)	
DFS Secondary Definition		
Events, n (%)	124 (59.9)	116 (56.0)
Median DFS (95% CI) ^a , months	11.07 (8.31, 16.89)	17.68 (14.06, 22.37)
HR (95% CI) ^b	0.81 (0.63, 1.04)	
SECONDARY ENDPOINTS		
NUTRFS		
Events, n (%)	114 (55.1)	105 (50.7)
Median NUTRFS (95% CI) ^a , months	13.86 (9.66, 25.66)	19.15 (16.07, 37.16)
HR (95% CI) ^b	0.81 (0.62, 1.05)	

Abbreviations: DFS = disease free survival, HR = hazard ratio, NUTRFS = non-urothelial tract recurrence free survival

^aBased on Kaplan-Meier Estimates

^bStratified Cox proportional hazard model. Hazard ratio is nivolumab over placebo

Safety

Nivolumab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, have resolved following initiation of appropriate medical therapy or withdrawal of nivolumab.

The overall safety profile of nivolumab as monotherapy has been previously assessed from a pooled dataset (n = 3319). The most frequent adverse reactions in the pooled dataset ($\geq 10\%$) were fatigue (28%), rash (17%), pruritus (13%), diarrhoea (13%) and nausea (11%). The majority of adverse reactions were mild to moderate in severity (Grade 1 or 2).

The safety profile of nivolumab in patients treated with adjuvant nivolumab for muscle invasive urothelial carcinoma was based on 351 patients treated with nivolumab 240 mg once every two weeks from one study submitted compared with 348 patients treated with placebo. The median duration of treatment was 8.77 months for the nivolumab arm and 8.21 months for the placebo arm.

The results for the nivolumab treated patients was also compared to the database of pooled nivolumab monotherapy from all previous nivolumab clinical studies (2,590 patients).

Adverse reactions were reported in almost all patients in both treatment arms (98.9% in nivolumab arm, 95.4% in placebo arm). The most common adverse reactions reported in Study CA209274 were pruritus (30.2%), diarrhoea (29.1%) and fatigue (27.4%).

The number of deaths was similar in both treatment arms and the most common cause of death was progression of disease. Two deaths were considered drug related: immune related pneumonitis and pneumonitis.

The most common serious adverse events were urinary tract infection (2.6%), malignant neoplasm progression (2.3%), intestinal obstruction (1.4%), acute kidney injury (1.4%) and sepsis (1.1%).

Overall, no new safety issues were identified and the safety profile was consistent with the previously documented safety profile of nivolumab monotherapy.

Other aspects

It is not clear at this stage whether patients will require testing of tumour samples for PD-L1 expression prior to adjuvant treatment of high risk MIUC.

Risk management plan

The sponsor is required to comply with product vigilance and risk minimisation requirements.

The TGA decided a new risk management plan (RMP) was not required (see TGA's guidance on ['when an RMP is required'](#)) for this submission as the population group is not considered significantly different to current treatment populations.

The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in [risk management plans for medicines and biologicals](#) and [the TGA's risk management approach](#). Information on the [Australia specific annex \(ASA\)](#) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

The proposed extension to the indications for Opdivo is as follows:

Opdivo, as monotherapy, is indicated for the adjuvant treatment of patients with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC.

While efficacy, assessed as improvement in the disease free survival (DFS) rate compared with placebo, has been demonstrated for patients with MIUC at high risk of recurrence after radical resection of MIUC, the major issues with the proposed extension to the indications are discussed below.

Identification of high risk of recurrence of urothelial carcinoma

The Delegate considers that the population eligible for nivolumab should be consistent with the population assessed for efficacy in the clinical study where higher risk was defined as either 1) ypT2-ypT4a or ypN+;^{14,15,16} for patients who received neoadjuvant cisplatin; or 2) pT3-pT4a or pN+;^{14,15,16} for patients who did not receive neoadjuvant cisplatin and who also either were ineligible for or refused adjuvant cisplatin.

The Delegate requests the Committee's consideration as to whether the specific definition of high risk should be included in the indication or identified only in the clinical trial description in the Product Information.

Identification of exploratory subgroups likely to have less benefit from treatment with nivolumab

Many subgroups were assessed for DFS as sensitivity/exploratory analyses of the whole study population and for the stratification subgroup of tumour PD-L1 $\geq 1\%$. These analyses showed a hazard ratio less than one for all subgroups except for patients with upper urothelial tract cancer (kidney pelvis and ureter). The initial (primary analysis) suggested that patients who did not receive prior cisplatin (as neoadjuvant therapy) because they were unwilling to receive it also did not benefit in terms of an increased median DFS rate compared to placebo, however the subsequent analysis showed the hazard ratio for median DFS for that subgroup had become less than one, indicating a higher median DFS in the nivolumab treated population.

While the sensitivity analyses of DFS were exploratory those with kidney pelvic and ureter tumour locations were the only group to not show a trend towards a higher median DFS with nivolumab compared to placebo. It is not usual to describe exploratory analyses of subgroups however given the disparity in DFS between those with upper versus lower urinary tract tumours the Committee is requested to consider whether the clinical trial description should refer to the absence of a trend towards benefit in those with upper urothelial tract carcinoma.

Similarly while a benefit in terms of higher median DFS was seen in those with tumour PD-L1 $< 1\%$ it was a considerably smaller benefit than was apparent for those with tumour PD-L1 $\geq 1\%$. While a clinically significant additional duration of DFS was demonstrated overall and for both PD-L1 subgroups the overall survival data is immature, and the study is ongoing.

The committee is requested to consider whether the exploratory DFS and overall survival results for these exploratory subgroups (comprising approximate 59% of the study population with PD-L1 $< 1\%$ and 21% of the study population with upper urothelial tract cancer) should be mentioned in the clinical trial description.

1. Proposition to include the test used to determine tumour PD-L1 percentage in the clinical trial description.

The Delegate requests the Committee comment on the availability of tumour PD-L1 testing being conducted in Australia, including the specific test applied in the clinical trial supporting the proposed indication.

2. Depiction of adverse reactions associated with nivolumab in the Product Information.

Nivolumab has current indications as monotherapy for adjuvant treatment in melanoma and oesophageal or gastro-oesophageal junction cancer as well as indications as monotherapy for melanoma, non-small cell lung cancer, clear cell renal cell carcinoma, classical Hodgkin's lymphoma, squamous cell cancer of the head and neck, hepatocellular carcinoma and oesophageal squamous cell carcinoma. Given the multiple indications for nivolumab the presentation of adverse reactions associated with monotherapy nivolumab has been combined

in a single table with no comparators and the incidence of only the most frequent adverse reactions is stated from the pooled studies with a range for incidence of individual adverse reactions of lower frequency. It is proposed that this presentation be amended to include the adverse reactions from monotherapy adjuvant MIUC. No new safety issues for nivolumab were identified in the study supporting the proposed extension of indications to MIUC.

With the combination of all adverse reactions from monotherapy nivolumab studies into a single table there is now no separate presentation of adverse reactions associated with nivolumab monotherapy given as adjuvant therapy as distinguished from monotherapy for advanced disease indications.

The Committee is requested to comment on the proposed presentation of adverse reactions for monotherapy nivolumab including whether there should be separate presentations for the adjuvant monotherapy indications in the PI.

Proposed action

The Delegate is inclined to approve the proposed extension of indications for Opdivo to include:

Opdivo, as monotherapy, is indicated for the adjuvant treatment of patients with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC.

The approval is conditional on the satisfactory negotiation of the Product Information, including the indication.

Advisory Committee considerations

The [Advisory Committee on Medicines \(ACM\)](#) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Identification of those considered to be at high risk of recurrence of urothelial carcinoma.

The Delegate requests the ACM's consideration as to whether the specific definition of high risk should be included in the indication or identified only in the clinical trial description in the Product Information.

The ACM was of the view that the population eligible for nivolumab should be consistent with the population assessed for efficacy in the clinical study where higher risk was defined as either 1) ypT2-ypT4a or ypN+;^{14,15,16} for patients who received neoadjuvant cisplatin; or 2) pT3-pT4a or pN+;^{14,15,16} for patients who did not receive neoadjuvant cisplatin and who also either were ineligible for or refused adjuvant cisplatin.

The ACM advised that it would be appropriate to define high risk by staging criteria in the Product Information (PI) and that this should be guided by the clinical trial entry criteria.

The ACM noted that this would be useful for prescribers as they will be aware of the stage of the disease.

The ACM discussed the overall survival rates noting that this data is immature. The ACM agreed that for adjuvant treatment overall survival data is critical, as within this setting the clinician's aim is often to increase overall survival. Noting the importance of the overall survival endpoint,

the ACM was supportive of the mature overall survival data being provided to the TGA once available and agreed with having this as a condition of registration.

The ACM also noted that there is not yet strong data in support of the use of nivolumab within upper urothelial tract cancers (renal pelvis and ureter) and agreed that this should be noted within the PI.

Overall, noting that much of the submitted data for this submission is early data, the ACM was of the view that the indication should remain as proposed and additional details be included within the PI at this time.

2. Identification of exploratory subgroups likely to have less benefit from treatment with nivolumab.

The ACM is requested to consider whether the exploratory disease-free survival and overall survival results for these exploratory subgroups (comprising around 59% of the Study CA209274 (CheckMate 274 trial) study population with PD-L1 < 1% and 21% of the study population with upper urothelial tract cancer) should be mentioned in the clinical trial description.

The ACM advised that while it appears there is greater benefit with higher PD-L1 expression, there is also evidence in the data to date of a broader benefit.

The ACM noted that the information currently available is early exploratory data and questioned whether it is appropriate to use this data within the PI to further define subgroups that would benefit from treatment with nivolumab. The ACM noted that the sample size for some tumours is not very large and there is currently a high level of uncertainty within this space.

The ACM reiterated that while disease-free survival is a relevant outcome, oncologists often refer to overall survival data and long-term toxicity when determining benefit risk profiles.

3. It is proposed that the test used to determine tumour PD-L1 percentage be included in the clinical trial description.

The Delegate requests the ACM to comment on the availability of tumour PD-L1 testing being conducted in Australia, including the specific test applied in the clinical trial supporting the proposed indication.

The ACM advised that PD-L1 tumour testing is widely available within Australia; it is considered to be the standard of care across a number of tumour types and is required to determine treatment options.

To assist in the management of the well-known variations with different antibodies, the ACM advised that the specific test used within the clinical trials (the PharmDx Dako IHC 28-8 and the associated PD-L1 criteria) should be listed within the clinical trials section of the PI.

4. Regarding the depiction of adverse events associated with nivolumab in the Product Information:

The ACM is requested to comment on the proposed presentation of adverse reactions for monotherapy nivolumab including whether there should be separate presentations for the adjuvant monotherapy indications in the Product Information.

The ACM agreed that a consolidated presentation of single agent toxicity is appropriate and noted that repeating the same information may dilute the meaning. The ACM however highlighted that the risk/benefit discussion is different in the adjuvant versus advanced disease setting where long term toxicity may have greater clinical relevance.

The ACM highlighted that it is important that the treating clinician engage in individualised risk/benefit discussions with the patient.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

Opdivo, as monotherapy, is indicated for the adjuvant treatment of patients with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Opdivo (nivolumab) 40 mg in 4 mL, 100 mg in 10 mL, 240 mg in 24 mL concentrated solution for infusion vial for the following extension of indications:

Opdivo, as monotherapy, is indicated for the adjuvant treatment of patients with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC.

Specific conditions of registration applying to these goods

- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The Product Information 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 [PI/CMI search facility](#).

Therapeutic Goods Administration

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<https://www.tga.gov.au>

Reference/Publication #