

6.05 NIVOLUMAB,

**Injection concentrate for I.V. infusion 40 mg in 4 mL,
Injection concentrate for I.V. infusion 100 mg in 10 mL,
Opdivo[®],
Bristol-Myers Squibb Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 100 (Efficient Funding of Chemotherapy Program) Authority Required listing for adjuvant treatment of patients who have 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.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus watchful waiting. The key components of the clinical issue are summarised in Table 1.

Table 1: Key components of the clinical issue addressed by the submission.

Component	Description
Population	Patients with muscle invasive urothelial carcinoma (MIUC) who have undergone radical resection surgery and are at high risk of recurrence
Intervention	Nivolumab
Comparator	Watch and wait surveillance
Outcomes	Disease-free survival (DFS), overall survival (OS), non-urothelial tract recurrence-free survival (NUTRFS), disease-specific survival (DSS), health-related quality of life (HRQoL), safety and tolerability.
Clinical claim	Nivolumab has superior efficacy and inferior safety compared to watchful waiting

Source: Table 1, p15 of the submission.

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** not registered. The submission was made under the TGA/PBAC Parallel Process. The TGA clinical evaluation report (Round 2 CER) and the TGA Delegate's overview (Submission PM-2021-02518-1-4, Date of Finalisation 06 May 2022) were received during the evaluation prior to PBAC consideration. The Delegate noted that while a decision was yet to be made, the Delegate was inclined to approve the registration of nivolumab, as monotherapy, for the adjuvant treatment of MIUC patients, who are at high risk of recurrence after undergoing radical resection of MIUC. The PBAC noted that the delegate sought advice on the submission at the June ACM meeting. The PBAC noted that the ACM was supportive of mature overall survival (OS) data being provided to the TGA once available and having this as a condition of registration. In addition, the ACM noted that there was not yet strong data in support of nivolumab within upper urothelial tract cancers and considered this should be noted within the Product Information (PI). The PBAC noted that the ACM considered nivolumab to have an overall positive benefit-risk profile for the indication specified by the Delegate.

2.2 Nivolumab monotherapy was registered by the TGA in February 2018 for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy. The approval was based on objective response rate and duration of response in a single arm study but is not PBS listed.

2.3 Table 2 summarises the regulatory status of nivolumab overseas for high risk MIUC.

Table 2: Summary of overseas regulatory approval status for nivolumab as an adjuvant treatment of high risk MIUC

	USA	European Union	Canada	Switzerland
Indication requested	Adjuvant treatment of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection	As monotherapy for the adjuvant treatment of adults with MIUC with tumour cell PD-L1 expression \geq 1%, who are at high risk of recurrence after undergoing radical resection of MIUC.	As monotherapy for the adjuvant treatment of patients with MIUC who are at high risk of recurrence after undergoing radical resection of MIUC.	Adjuvant treatment of adult patients with MIUC who are at high risk of recurrence after undergoing radical resection of MIUC.
Anticipated approval date	Approved 20-August-2021	Positive opinion adopted by the EMA on 24 th February 2022.	31-May-2022	07-January-2022

Source: Table 8, p38 of the submission.

EMA = European Medicines Agency; MIUC = muscle invasive urothelial carcinoma; USA, United States of America

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT Form	PBS item code	Maximum amount	No. of Repeats	Dispensed price for maximum amount
NIVOLUMAB Injection	New (Public) New (Private)	480 mg	5 (initial treatment) 6 (continuing treatment)	Published price \$ [redacted] (Private Hospital) \$ [redacted] (Public Hospital) Effective price \$ [redacted] (Private Hospital) \$ [redacted] (Public Hospital)
Available brands				
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)				
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)				
Restriction Summary / Treatment of Concept: [New 1]				
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals				
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)				
<i>Episodicity: [blank]</i>				
<i>Severity: [blank]</i>				

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Condition: Urothelial carcinoma
Indication: Urothelial carcinoma Muscle-invasive urothelial carcinoma at high risk of recurrence after radical resection
Treatment Phase: [blank] Initial treatment
Clinical criteria: The treatment must be for each of: (i) adjuvant therapy that initiates within 120 days of radical surgical resection, (ii) muscle invasive type disease, (iii) disease considered to be, by the treating physician, at high risk of recurrence, but yet to recur, (iv) use as the sole PBS-subsidised anti-cancer treatment, (v) dosing in accordance with a dosing regimen specified in the drug's approved Australian Product Information
Treatment criteria: Patient must be undergoing treatment that is each of: (i) initial PBS-subsidised treatment with this drug, (ii) initiated in a patient untreated with programmed cell death-1/ligand-1 (PD-1/PDL-1) inhibitor therapy, (iii) occurring in a patient with a WHO performance status no greater than 1 at treatment initiation with this drug; or Patient must be undergoing treatment that is each of: (i) continuing PBS-subsidised treatment with this drug, (ii) does not extend treatment duration beyond 12 months of uninterrupted, continuous treatment from the first administered dose
Administrative Advice: An increase in repeat prescription numbers, up to a value of 11, may only be sought where the prescribed dosing frequency is fortnightly.
Administrative Advice: Special Pricing Arrangements apply.
Clinical criteria: Patient must have pathologically confirmed urothelial carcinoma (originating in the bladder, renal pelvis or ureter) at high risk of recurrence based on pathologic staging of radical surgery tissue, classified as either: ypT2-pT4a or ypN+ (where neoadjuvant chemotherapy has been given) / pT3-pT4a or pN+ (where no neoadjuvant chemotherapy has been given). AND The treatment must be adjuvant to complete surgical resection. AND The treatment must commence within 120 days of radical resection. AND Patient must have a WHO performance status of 0 or 1. AND Patient must not have experienced disease recurrence. AND The treatment must be the sole PBS-subsidised therapy for this condition. AND Patient must not have received prior PBS-subsidised treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition.
Treatment criteria: Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks.
Prescribing Instructions: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. No increase in the maximum quantity or number of units may be authorised. Up to 12 repeats may be sought if dosing at 240 mg every 2 weeks. The treatment must not exceed 12 months for this PBS indication.
Treatment Phase: Continuing treatment
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition. AND Patient must not have experienced disease recurrence. AND The treatment must be the sole PBS-subsidised therapy for this condition.
Treatment criteria: Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks.
Prescribing Instructions: No increase in the maximum quantity or number of units may be authorised.

<p>Up to 12 repeats may be sought if dosing at 240 mg every 2 weeks. The treatment must not exceed 12 months for this PBS indication.</p>

- 3.2 The submission proposed a special pricing arrangement (SPA) with an effective Public hospital DPMA of \$| (published \$|) and an effective Private hospital DPMA of \$| (published \$|).
- 3.3 The nivolumab dosage in the key CM274 trial was 240 mg every 2 weeks (Q2W) until disease recurrence or unacceptable toxicity, with a maximum treatment duration of one year. The recommended nivolumab monotherapy dosing regimens for the proposed indication in the updated PI are 240 mg Q2W or 480 mg every 4 weeks (Q4W). The submission noted that the two flat dosing regimens for nivolumab were recommended and subsequently listed on the PBS (August 2019) for all existing PBS indications for nivolumab use as monotherapy. The proposed maximum amount of nivolumab for this indication was 480 mg, accommodating the longer interval of the Q4W dosing regimen.
- 3.4 The submission proposed 5 repeats for the initial treatment phase and 6 repeats for the continuing treatment phase which allows a total of 12 months of treatment with the Q4W dosing regimen. The submission noted that prescribing instruction were included in the restriction to accommodate the Q2W dosing regimen. The requested number of repeats was slightly higher than that in the current listing for adjuvant nivolumab in the treatment of resectable melanoma (5 for initial and 5 for continuing), with administrative advice stating that no increase in the maximum number of repeats may be authorised. The PBAC noted the administrative advice proposed by the Secretariat allowing 11 repeat prescriptions where the dosing is Q2W would provide treatment for 6 months and considered this was appropriate.
- 3.5 The submission requested an Authority required (Telephone/Online) listing for patients with high risk MIUC after radical resection. The rationale in the submission for this request was to ensure consistency with the current PBS listings for adjuvant nivolumab use in melanoma.
- 3.6 The PBAC also considered that a broad PBS indication of ‘urothelial carcinoma’ was acceptable and that limiting treatment according to initial tumour origin was not appropriate given the small sample size and low number of events informing this subgroup analysis in the CM274 trial (see paragraph 6.22).
- 3.7 The PBAC considered a single restriction for initial and continuing treatment as proposed by the Secretariat appropriate.
- 3.8 The proposed initial treatment restriction included clinical criteria for pathological staging. The PBAC considered that removal of reference to the pathologic staging categories was appropriate, noting the staging categories were not detailed in the proposed TGA indication. The PBAC also considered it appropriate to remove reference to pathologically confirmed urothelial carcinoma and to retain the requirement that a patient must have a WHO performance status of no greater than 1 at the time of treatment initiation. However, as no clear improvement in disease free survival (DFS) was observed with nivolumab over placebo in patients who had not received prior neoadjuvant cisplatin-based chemotherapy, the PBAC recommended

limiting treatment to patients who had received prior neoadjuvant chemotherapy (see paragraph 6.21).

- 3.9 The PBAC considered that the prescriber instruction for a confirmatory scan, taken at least 4 weeks after progression / transient tumour flare, was not relevant to adjuvant use and recommended it be removed from the proposed restriction.
- 3.10 The PBAC considered that immunotherapy should be restricted to one course of treatment per lifetime given the paucity of clinical and economic evidence available to support retreatment. The PBAC considered the proposed listing of nivolumab for adjuvant use may necessitate flow-on restriction changes to the current listings for programmed cell death (ligand)-1 (PD-L1/PD-1) inhibitors in urothelial carcinoma (UC) to prevent sequential use of these agents.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Bladder cancer is the eleventh most diagnosed cancer in Australia with 25% cases involving muscle invasive disease at diagnosis. UC arises from urothelial cells of the transitional epithelium which lines the renal pelvis, ureters, urinary bladder, and urethra.
- 4.2 MIUC encompasses both muscle invasive bladder cancer (MIBC) and UTUC. More than 90% of urothelial tumours originate in the urinary bladder, with the remaining tumours originating in the renal pelvis (~8%), ureter or urethra (~2%)*. Although the majority of patients present with non-invasive disease, 15% to 25% of UCs either present with or eventually progress to muscle invasive or metastatic disease.
- 4.3 Patients with MIBC are at a high risk for developing metastatic disease, even after undergoing radical cystectomy. Moreover, despite multimodal treatment (surgery ± radiotherapy/chemotherapy), more than 50% of patients with MIBC will eventually develop metastases. The prognosis of metastatic disease is poor, with a median OS of up to 15 months with chemotherapy alone, and up to 21 months when maintenance immunotherapy is added in the first-line setting. Similar to MIBC, the prognosis of muscle invasive UTUC is poor with a 5-year disease-specific survival of less than 50% (p22, Round 2 TGA CER for nivolumab, Submission PM-2021-02518-1-4).
- 4.4 Current staging of UC uses the tumour-node-metastasis (TNM) system of the American Joint Committee on Cancer (AJCC, 8th edition, 2017). Classification of high risk of recurrence in the requested restriction was based on pathological staging of radical surgery tissue, as either ypT2-pT4a or ypN+ (where neoadjuvant chemotherapy has been given) OR pT3-pT4a or pN+ (where no neoadjuvant chemotherapy has been given). This is consistent with current National Comprehensive Cancer Network Guidelines (NCCN, Version 1.2022) except that the guidelines specify platinum-based neoadjuvant therapy.

* Rouprêt M et al. EAU guidelines on upper urinary tract urothelial carcinoma. Disease management [Internet] Arnhem, The Netherlands. European Association of Urology. 2019.

- 4.5 The submission positioned nivolumab as an alternative to watchful waiting in the high risk MIUC adjuvant setting after radical surgery regardless of cisplatin-eligibility or receipt of prior neoadjuvant chemotherapy.
- 4.6 The sponsor’s advisory board reported that of patients with MIUC, approximately 90–95% would have a radical cystectomy. Feedback from the Genitourinary Advisory Board virtual meeting (p15, BMSA GU Advisory Board Minutes 2021, Attachment 1 to the main submission) indicated that there were relatively few cisplatin-ineligible MIUC patients in clinical practice.
- 4.7 Recognising that there may be some variation in clinical practice, current clinical management guidelines for MIUC differ based on the primary tumour site (urinary bladder versus upper tract renal pelvis/ureter).
- For high risk muscle invasive UTUC, the European Association of Urology (EAU) guidelines recommend postoperative platinum-based adjuvant chemotherapy to eligible patients[†]. These recommendations are based mainly on results from the randomised POUT[‡] trial which showed that, compared to surveillance, adjuvant platinum-based chemotherapy improved both DFS and metastasis free survival in patients with muscle invasive or lymph node positive UTUC.
 - For high risk MIBC, the EAU guidelines recommend neoadjuvant cisplatin-based chemotherapy to eligible patients[§]. Except in uncommon circumstances, patients who have received neoadjuvant platinum-based chemotherapy are unlikely to be offered adjuvant platinum-based chemotherapy.
- 4.8 Nivolumab is a fully human immunoglobulin G4 monoclonal antibody which binds to the PD-1 receptor on T-cells. It acts as an immunomodulating agent by blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2.
- 4.9 The PBAC noted that atezolizumab (a PD-L1 inhibitor) has been assessed as an adjuvant treatment in a similar patient population with MIUC after radical cystectomy or nephroureterectomy (IMvigor010).^{**} The observation-controlled randomised trial recruited patients who had ypT2–4a or ypN+ tumours following neoadjuvant chemotherapy or pT3–4a or pN+ tumours if no neoadjuvant chemotherapy was received. 406 patients were assigned to the atezolizumab group and 403 were assigned to the observation group. The median duration of follow-up was 21.9 months. The median DFS duration was 19.4 months (95% CI: 15.9, 24.8) with atezolizumab and 16.6 months (95% CI: 11.2, 24.8) with observation (stratified HR 0.89; (95% CI: 0.74, 1.08); p=0.24). The PBAC noted that the results did not support the use of atezolizumab in the trial population and considered that this indicated that there may be a lack of a class effect for PD-L1 inhibitor therapy.

[†] European Association of Urology (<https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma/chapter/disease-management>)

[‡] Birtle et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *The Lancet*. 2020, (395), Issue 10232, pp1268-77

[§] European Association of Urology (<https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer/chapter/disease-management>)

^{**} Bellmunt J, Hussain M, Gschwend JE, Albers P, Oudard S, Castellano D, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology*. 2021 2021/04/01;;22(4):525-37.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated 'watch and wait' surveillance (herein referred to as watchful waiting) as the main comparator. The submission noted that cisplatin-based adjuvant chemotherapy was of "limited relevance and not a relevant comparator". The main arguments provided in support of this nomination were that:

- Based on international guidelines and advice from a Genitourinary Advisory Board virtual meeting (8th October 2021), watchful waiting is recommended following neoadjuvant chemotherapy.
- There are limited data and currently there is debate to support the role of adjuvant chemotherapy to treat high-risk MIUC, even for patients who have not received neoadjuvant chemotherapy.
- Clinical Registry data^{††} for MIUC patients from multiple centres in Australia (BLADDA registry N = 368; median follow-up duration of 23 months) indicated that of 238 patients who underwent a surgery-based treatment approach, the most common treatment approach consisted of 'watch and wait' surveillance with surgery only (40%); neoadjuvant chemotherapy with surgery (35%), while a "minority" of patients (25%) received adjuvant treatment post-surgery.
- As the CM274 trial did not include adjuvant chemotherapy as a comparator, an indirect comparison would be required for the subgroup of patients who were eligible for adjuvant cisplatin-based chemotherapy. However, due to significant limitations within the evidence base relating to the chemotherapy trials (between-study heterogeneity, small sample sizes, statistical and design flaws), results would be subject to considerable uncertainty and would not be suitable to inform decision-making.

5.2 The nominated comparator of 'watch and wait' would be better described as 'active surveillance' given that the patients are closely monitored and a proportion would receive medical interventions as required. Watchful waiting is an appropriate comparator for patients who would otherwise not be offered/treated with adjuvant chemotherapy. This population would likely comprise of patients who would have received neoadjuvant chemotherapy such as patients with MIBC (and thus unlikely to be offered further treatment with adjuvant platinum-based chemotherapy) or patients who would be considered ineligible for adjuvant platinum-based treatment based on several clinical factors (such as sub-optimal creatinine clearance, hearing loss, peripheral neuropathy, and poor performance status).

5.3 Adjuvant platinum-based chemotherapy is a relevant comparator in eligible patients who have not received neoadjuvant chemotherapy:

- From clinician responses provided to a Pre-Advisory Board Survey^{††}, the expected proportion of high risk MIUC patients, who are currently treated with adjuvant

^{††} Tran, B. (2022). BLADDA - Bladder and Urothelial Cancer Data and Biobank, Data Report. References folder (Part 3) accompanying the submission.

^{††} "All Responses to Pre-Advisory Board Survey 2021", Excel spreadsheet, Attachment 1 to the main submission

chemotherapy, varied considerably from 25% to 70%, with some clinicians indicating that adjuvant chemotherapy is offered to almost all patients who had not received neoadjuvant chemotherapy.

- Feedback from the Genitourinary Advisory Board virtual meeting suggested that a reasonable assumption for the proportion of high risk MIUC patients, who are treated with adjuvant chemotherapy, was 36% with 64% of patients on watch and wait surveillance. There was also a consensus among the clinicians that in high risk muscle-invasive UTUC, neoadjuvant chemotherapy generally should not be offered, and that there was stronger evidence for adjuvant chemotherapy based on the POUT study. This consensus aligns with current EAU clinical management guidelines. It was also noted that in the majority of cases, patients are offered upfront neoadjuvant chemotherapy for UC in the bladder and in most cases adjuvant chemotherapy is offered for UTUC^{§§}.

The Pre-Sub-Committee Response (PSCR) reiterated that ‘watch and wait’ was nominated as the main comparator as most patients in clinical practice either receive neoadjuvant cisplatin-based chemotherapy and therefore do not receive further adjuvant chemotherapy, or they are cisplatin-ineligible and are unable to receive cisplatin-based adjuvant chemotherapy. The PSCR stated that international guidelines advise that adjuvant chemotherapy is not preferred for patients who do not receive neoadjuvant therapy as it remains an area of debate due to a poor evidence base. For these reasons, the PSCR argued that cisplatin-based chemotherapy is not a relevant comparator. The ESC noted that there remains a proportion of MIUC patients in clinical practice who do not receive neoadjuvant chemotherapy and go on to receive adjuvant chemotherapy in accordance with the favoured treatment protocol for these patients in the NCCN guidelines^{***} and therefore agreed with the evaluation that platinum-based chemotherapy remained a relevant comparator for these patients. It was maintained in the pre-PBAC response that ‘watch and wait’ surveillance was the relevant comparator for adjuvant nivolumab. It was reiterated that an indirect comparison of nivolumab versus chemotherapy in the adjuvant setting would be subject to considerable uncertainty and not suitable to inform decision-making. The PBAC considered that watchful waiting was appropriate if treatment was restricted to those who had received neoadjuvant chemotherapy.

- 5.4 The use of nivolumab in the adjuvant setting could result in downstream consequences to other PBS-listed medicines, including pembrolizumab, which is PBS-listed for the treatment of locally advanced or metastatic UC in patients who have experienced disease progression following treatment with platinum-based chemotherapy. Avelumab was also recently recommended as maintenance therapy in the advanced UC setting (Avelumab Public Summary Document (PSD), March 2021 PBAC Meeting).

For more detail on PBAC’s view, see section 7 PBAC outcome.

^{§§} Pages 8-11, Genitourinary Ad Board Summary; ONC-AU-2100418; Attachment 1 to the main submission.

^{***} NCCN. (2021). NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer Version 5.2021.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comment from a health care professional indicated a substantial proportion of patients are ineligible to receive neoadjuvant chemotherapy due to comorbidities and suggested that nivolumab is a well tolerated treatment that demonstrates improvement in DFS after surgery. The comment from BEAT Bladder Cancer Australia highlighted the effects of the disease itself and its treatment on health-related quality of life (HRQoL) combined with the effects of the poor prognosis and fear of recurrence. They suggested that the life improvements that matter most to those with high-risk MIUC centred around patient empowerment in becoming more independent, relying less on carers and having choices about treatment options. BEAT Bladder Cancer Australia suggested nivolumab offered improvements in these areas and enhanced HRQoL with greater chance of DFS particularly for those unable to have chemotherapy.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the nivolumab submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the CM274 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for nivolumab, which was a Grade A. This is the highest grade on a scale from A to C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies.^{†††}

Clinical trials

6.4 The submission was based on one head-to-head double blind randomised trial (CM274) comparing adjuvant treatment with nivolumab (240 mg Q2W; N = 353) with placebo (N = 356) in patients with high risk MIUC who had undergone radical surgery.

6.5 Details of the key CM274 trial are provided in Table 3.

^{†††} Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CA209274 (CheckMate 274 (CM274)) (NCT02632409)	Primary Clinical Study Report BMS-936558. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High risk Invasive Urothelial Carcinoma.	4 December 2020.
	Erratum to Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High risk Invasive Urothelial Carcinoma	5 May 2021
	Bajorin, D F., et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma.	New England Journal of Medicine 2021; 384(22), 2102-2114.
	Galsky, DM., et al. Disease-free survival with longer follow-up from the phase 3 CheckMate 274 trial of adjuvant nivolumab in patients who underwent surgery for high risk muscle-invasive urothelial carcinoma.	Society of Urology Oncology (SUO) 22 nd Annual Meeting, December 1–3, 2021.

Source: Table 2.4, p28 of the submission

6.6 The key features of the CM274 trial are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Nivolumab versus placebo (proxy for watchful waiting)						
CM274	709	R ^a , DB Median follow-up NIVO: 24.44 months; PBO: 22.51 months (Data cutoff with data cutoff 01-February-2021)	Low	<u>Adjuvant setting</u> Undergone radical surgical resection for MIUC. Prior neoadjuvant cisplatin chemotherapy: Stage ypT2-ypT4a or ypN+; No prior neoadjuvant cisplatin and were ineligible/declined adjuvant cisplatin chemotherapy: pT3-pT4a or pN+	Primary: DFS Secondary: NUTRFS, OS, and DSS Exploratory: DMFS <u>Primary analysis populations:</u> ITT and the PD-L1 ≥ 1% subgroup	Only trial-based DFS data used

Source: Table 23, p61 and Section 2.4.3 of the submission and the Round 2 clinical evaluation report for nivolumab (Submission PM-2021-02518-1-4

NIVO = nivolumab; PBO = placebo; PD-L1 = programmed cell death ligand 1; DB = double blind; DSS = disease specific survival; DFS = disease free survival; DMFS = distant metastasis-free survival; NUTRFS = non upper tract recurrence free survival; DSS = disease specific survival; OS = overall survival; R = randomised.

^aStratification factors at randomisation were: pathologic nodal status (N+ vs. N0/x with < 10 nodes removed vs N0 with ≥ 10 nodes removed); tumour cell PD-L1 expression (≥ 1%, < 1% or indeterminate); and prior use of cisplatin neoadjuvant chemotherapy (yes vs no).

6.7 The CM274 trial recruited patients who had undergone radical surgical resection (R0, negative margins) for MIUC, originating in the bladder, ureter or renal pelvis, and who were considered at high risk of disease recurrence. The number of subjects enrolled with UTUC was capped at 20% to “prevent substantial deviation from the natural prevalence of bladder disease (80%) as compared with upper tract disease”.

6.8 High risk of recurrence based on pathological staging of radical surgery tissue was as follows:

- Patients who received neoadjuvant cisplatin chemotherapy: ypT2-ypT4a or ypN+; or

- Patients who had not received and were ineligible for neoadjuvant cisplatin chemotherapy: pT3-pT4a or pN+ and not eligible for/declined adjuvant cisplatin chemotherapy.
- 6.9 The key factors relating to ineligibility for cisplatin-based chemotherapy were: i) creatinine clearance of < 60 mL/min, ii) ≥ Grade 2 audiometric hearing loss and peripheral neuropathy, iii) ECOG PS score of 2, and iv) New York Heart Association Class III or IV Heart Failure.
- 6.10 Patients who were eligible for cisplatin chemotherapy could be enrolled if they refused available adjuvant chemotherapy, despite being informed by the investigator about treatment options. Patients were excluded from the CM274 trial if they had previously undergone a partial cystectomy or partial nephrectomy, received adjuvant systemic therapy, or radiation therapy after radical surgery.
- 6.11 Stratification factors in the CM274 trial were: pathologic nodal status (N+ vs. N0/x with < 10 nodes removed vs N0 with ≥ 10 nodes removed); tumour cell PD-L1 expression (≥ 1%, < 1% or indeterminate); and prior use of cisplatin neoadjuvant chemotherapy (yes vs no). Less than 2% of patients enrolled in the CM274 trial were classified as PD-L1 indeterminate or not evaluable.
- 6.12 The primary analysis populations were the intention to treat (ITT) and PD-L1 ≥ 1% subgroup populations. The primary endpoint was DFS. Secondary and exploratory endpoints included OS, non-urothelial tract recurrence-free survival (NUTRFS) and distant metastasis-free survival (DMFS).
- 6.13 There were limited data provided in the submission on subsequent anti-cancer treatments in CM274. Table 5 presents a summary of subsequent anti-cancer treatments reported for the nivolumab and placebo arms in the CM274 trial. The proportion of patients by type of subsequent therapy was based on the number of patients randomised.

Table 5: Subsequent anti-cancer therapies in the CM274 trial – ITT population

Type of subsequent therapy	Nivolumab (N=353)	Placebo (N=356)
	n (% of randomised)	n (% of randomised)
Any ^a	124 (35.1%)	145 (40.7%)
Radiotherapy	22 (6.2%)	29 (8.1%)
Surgery	14 (4.0%)	15 (4.2%)
Systemic therapy	105 (30.0%)	134 (37.6%)
Immunotherapy ^b	28 (7.9%) 18% of patients who recurred (28/153)	85 (23.9%) 44% of patients who recurred (85/193)
Patients with > 1 dose of subsequent intravesical chemotherapy	4 (1.1%)	9 (2.5%)
Patients with 1 dose of subsequent intravesical chemotherapy	5 (1.4%)	4 (1.1%)

Source: Table 22, p60 of the submission.

ITT = intention to treat.

Data based on February 2021 data cutoff

^a Patients may have received more than one type of subsequent therapy. Subsequent therapy was primarily based on recurrence.

^b The most frequent subsequent immunotherapies received were pembrolizumab, atezolizumab, and nivolumab. Specific proportions were not reported.

- 6.14 Among all randomised subjects, subsequent anti-cancer therapy was received by 35.1% of patients in the nivolumab arm and 40.7% of patients in the placebo arm. The

most common form of subsequent anti-cancer therapy was systemic therapy (30.0% in the nivolumab arm and 37.6% patients in the placebo arm). Subsequent immunotherapy was received by 8% and 24% of patients in the nivolumab and placebo arms, respectively. The most frequent subsequent immunotherapies received were pembrolizumab, atezolizumab, and nivolumab. No further details were provided in the submission.

- 6.15 Among patients who experienced recurrence (estimated as the number of patients with a DFS event minus the number of pre-recurrence deaths), approximately 18% (28/153) and 44% (85/193) of patients received immunotherapy in the nivolumab and placebo arms, respectively. This pattern of use of subsequent anti-cancer therapies between treatment arms in CM274 does not appear to reflect the expected use of subsequent anti-cancer treatment in Australian clinical practice. Sequential use of immunotherapy as observed for the nivolumab arm is not indicated in Australian clinical practice. It is also uncertain whether subsequent use of immunotherapy in the placebo arm is reflective of expected use in clinical practice where prior use of platinum-based chemotherapy is required to be eligible for a PD-(L)1 inhibitor, either in the first-line maintenance setting with avelumab (recently recommended^{***}) or in the second-line setting after failure on platinum-based chemotherapy. The ESC agreed with the evaluation that the subsequent use of immunotherapy in the CM274 trial does not reflect clinical practice in Australia. Immunotherapy is typically restricted to one regimen for a patient's entire treatment course. Furthermore, the use of immunotherapy post radical cystectomy could not be administered prior to receiving platinum-based chemotherapy. The ESC considered the overall impact of subsequent anti-cancer treatments in CM274 on the DFS and OS results remained unclear from the available data.

Comparative effectiveness

- 6.16 Results for the primary endpoint of DFS in the primary analysis populations (ITT and PD-L1 \geq 1% subgroup) are summarised in Table 6. The corresponding Kaplan-Meier (KM) curves are presented in Figure 1 and Figure 2. The DFS results are for the 1 February 2021 data cutoff.

^{***} Avelumab Public Summary Document– March 2021 PBAC Meeting

Table 6: CM274 - DFS results in the ITT and PD-L1 positive populations

DFS parameters	ITT population		PD-L1 ≥ 1% subgroup	
	NIVO (N=353)	PBO (N=356)	NIVO (N=140)	PBO (N=142)
Events, n (%)	175 (49.6%)	213 (59.8%)	56 (40.0%)	85 (59.9%)
Disease at baseline ^a				
Recurrence ^a				
Distant				
Local non-urothelial tract				
Local urothelial tract invasive				
Local urothelial tract non-invasive				
Death ^a				
Median DFS (95% CI), months ^b	22.0 (17.7, 36.9)	10.9 (8.3, 14.0)	NE (22.1, NE)	8.4 (5.6, 20.0)
HR ^c (95% CI)	0.70 (0.57, 0.85)		0.53 (0.38, 0.75)	
Stratified log-rank p-value ^d	0.0005		0.0002	
Disease free survival rates^b				
At 6 months, % (95% CI)	75.0% (70.1, 79.3)	60.5% (55.1, 65.4)	74.5% (66.2, 81.1)	55.7% (46.8, 63.6)
At 12 months, % (95% CI)	63.5% (58.1, 68.4)	46.9% (41.5, 52.1)	67.6% (59.0, 74.9)	46.3% (37.6, 54.5)
At 18 months, % (95% CI)	55.6% (50.0, 60.8)	42.5% (37.2, 47.8)	65.0% (56.2, 72.5)	42.1% (33.5, 50.4)
At 24 months, % (95% CI)	48.2% (42.4, 53.7)	38.7% (33.4, 44.1)	58.6% (49.3, 66.9)	37.4% (29.0, 45.8)
At 30 months, % (95% CI)	44.9% (39.0, 50.7)	35.5% (30.1, 40.9)	53.1% (43.5, 62.3)	33.6% (25.2, 42.3)

Source: Table 43, p107 of the Round 2 TGA clinical evaluation report (Submission PM-2021-02518-1-40); Table 27, p71 of the submission; Table S.5.26.1 CM274 clinical study report

CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; ITT = intention to treat (all randomised patients); NE = not estimable (not reached); NIVO = nivolumab; PBO = placebo; PD-L1 = programmed cell death ligand 1

Notes: Updated Analysis 19-May-2021 database lock with data cutoff 01-February-2021 provided to the TGA.

The median follow-up durations were 24.44 months and 22.51 months for all randomised patients in the nivolumab and placebo arms, respectively, and 25.53 months and 22.37 months for the PD-L1 ≥ 1% population in the nivolumab and placebo arms, respectively.

DFS was defined as the time between the date of randomisation and the date of first recurrence (local recurrence in the urothelial tract, local recurrence outside the urothelial tract, or distant recurrence) or death, whichever occurred first

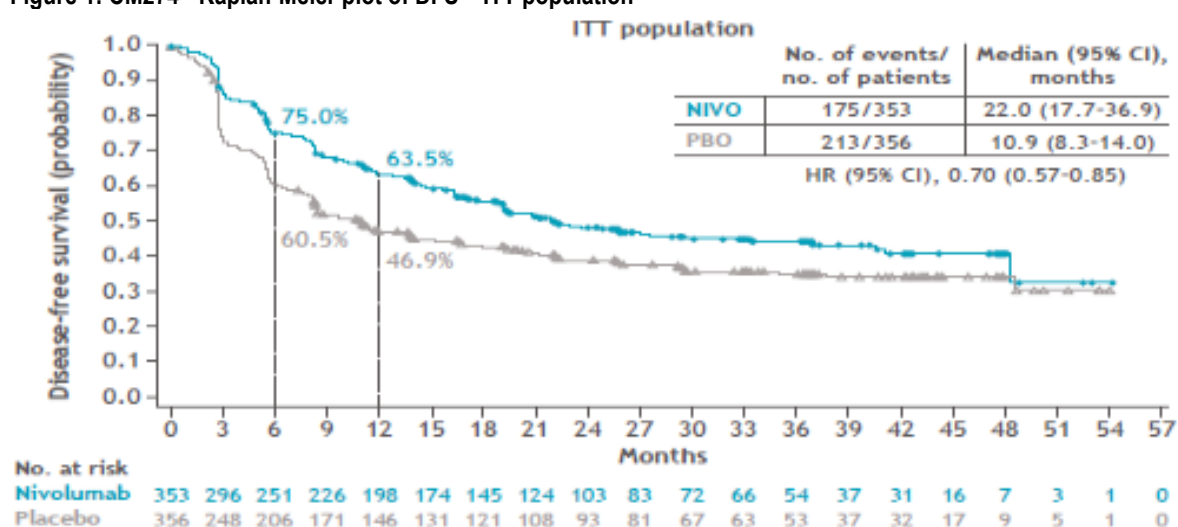
^a Based on all randomised subjects

^b Based on KM estimates

^c Stratified Cox proportional hazard model. HR is NIVO over PBO.

^d 2 sided p values from stratified regular log-rank test. For the ITT, log-rank test stratified by prior neoadjuvant cisplatin, pathological nodal status, and PD-L1 status (≥1% versus <1% / indeterminate). For the PD-L1 ≥ 1%, log-rank test stratified by prior neo-adjuvant cisplatin and pathological nodal status

Figure 1: CM274 - Kaplan-Meier plot of DFS – ITT population



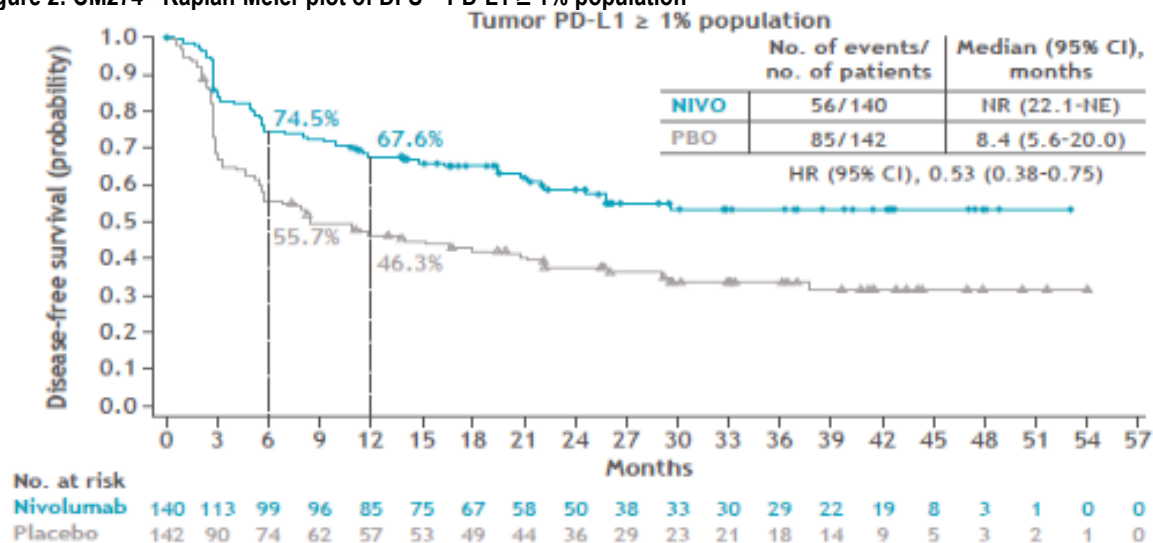
Source: Figure 12, p72 of the submission.

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; NIVO = nivolumab; PBO = placebo; DFS = disease free survival;

Notes: Data cutoff on 01-Feb-2021.

Statistical model for HR and p-value - stratified Cox proportional hazard and stratified log-rank test. Symbols represent censored observations.

Figure 2: CM274 - Kaplan-Meier plot of DFS – PD-L1 ≥ 1% population



Source: Figure 12, p72 of the submission.

CI = confidence interval; DFS = disease free survival; HR = hazard ratio; NR = not reached; NE = not estimable; NIVO = nivolumab; PBO = placebo; PD-L1 = programmed cell death ligand 1.

Notes: Data cutoff on 01-Feb-2021.

Statistical model for HR and p-value - stratified Cox proportional hazard and stratified log-rank test. Symbols represent censored observations

- 6.17 The median duration of follow-up for the ITT population was 24.4 months in the nivolumab arm and 22.5 months in the placebo arm. The median duration of DFS was 22.0 months in the nivolumab arm (95% confidence interval (CI): 17.7, 36.9) and 10.9 months in the placebo arm (95% CI: 8.3, 14.0). This difference (11.1 months) corresponded to a statistically significant 30% reduction in the hazard of recurrence or death favouring nivolumab (hazard ratio (HR) 0.70, 95% CI: 0.57, 0.85). At 30 months, the DFS rates (KM event free rates) were approximately 44.9% and 35.5% (difference of 9.4%) in the nivolumab and placebo arms, respectively.
- 6.18 The median duration of follow-up for the PD-L1 ≥ 1% population was 25.5 months in the nivolumab arm and 22.4 months in the placebo arm. The treatment effect associated with nivolumab was larger in this subgroup than in the ITT population. The median duration of DFS was not reached in the nivolumab arm (95% CI: 22.1, not reached) and was 8.4 months (95% CI: 5.6, 20.0) in the placebo arm. This corresponded to a statistically significant 47% reduction in the hazard of recurrence or death favouring nivolumab (HR 0.53, 95% CI: 0.38, 0.75).
- 6.19 In response to clinical questions from the TGA clinical evaluator during the Round 1 evaluation, the sponsor provided additional DFS data for the PD-L1 < 1% subgroup of the CM274 trial (data cutoff 1 February 2021, p99 of the Round 2 CER, Submission PM-2021-02518-1-4). This subgroup comprised approximately 1/3 of the ITT population. The results indicated a 15% treatment effect (HR 0.80, 95% CI: 0.62, 1.03) compared to that observed in the PD-L1 positive subgroup. The median duration of DFS for the PD-L1 < 1% subgroup was however much longer in the nivolumab arm compared to the placebo arm (17.7 months (95% CI: 14.1, 22.4) versus 11.1 months (95% CI: 8.3, 16.9)).

- 6.20 Additional subgroup analyses of DFS indicated that the HRs favoured nivolumab over placebo for most characteristics except for patients who had no prior use of neoadjuvant cisplatin-based chemotherapy and patients with upper urothelial cancers (renal pelvis or the ureter as the primary origin of the tumour):
- Use of prior neoadjuvant cisplatin therapy:
 - Yes (N = 308): HR = 0.52 (95% CI: 0.39, 0.71);
 - No (N = 401): HR = 0.90 (95% CI: 0.68, 1.18).Use of prior neoadjuvant cisplatin-based chemotherapy was a stratification factor at randomisation (Yes vs. No) in the CM274 trial.
 - Initial tumour origin:
 - Urinary bladder (N = 560): HR = 0.61 (95% CI: 0.49, 0.77);
 - Combined UTUC (N = 149; renal pelvis or ureter): HR = 1.34 (95% CI: 0.84, 2.44):
 - Ureter (N = 53): HR = 1.54 (95% CI: 0.69, 3.44).
 - Renal pelvis (N = 96): HR = 1.25 (95% CI: 0.70, 2.25).
- 6.21 No clear DFS benefit was observed with nivolumab over placebo in patients who had not received neoadjuvant cisplatin-based chemotherapy. This is noteworthy given that a significant number of patients who would be treated with nivolumab may not have received neoadjuvant cisplatin-based chemotherapy. One probable reason for the apparent lack of benefit in patients who had not received neoadjuvant cisplatin-based chemotherapy, although inconclusive, is that there was no “chemotherapy priming” to enhance the activity of immunotherapy. The PSCR stated that, while not statistically significant, the improvement in DFS observed in the non prior cisplatin group still reflected a treatment benefit in favour of nivolumab over placebo. The ESC agreed with the evaluation that there was no clear adjuvant nivolumab treatment effect among patients who had not received neoadjuvant chemotherapy. The ESC considered it was unclear if nivolumab would provide a benefit over adjuvant platinum-based chemotherapy in this subgroup of patients (see paragraph 5.3). The pre-PBAC response maintained the position held in the PSCR (see above and paragraph 6.40).
- 6.22 For UTUC patients, the DFS HR point estimates indicated that nivolumab may be potentially inferior to placebo. The DFS results favoured nivolumab only in MIBC patients. These results should be interpreted with caution given the small sample size of this subgroup. Nevertheless, it is possible that the underlying reason for an apparent lack of DFS benefit in UTUC patients was that the majority of these patients had not been offered prior neoadjuvant cisplatin-based chemotherapy as per management guidelines. The ESC considered these findings raise some uncertainty regarding the use of nivolumab in UTUC patients. However, the ESC agreed with the PSCR that the small sample sizes and a low number of events mean that it cannot be reliably concluded that patients with UTUC tumours are different from the whole study population.
- 6.23 OS data were not provided in the submission although data were available in the TGA Round 2 CER for nivolumab. The follow-up for OS is ongoing. A second interim analysis and a final analysis for the ITT population are anticipated in [redacted] and [redacted], respectively. The corresponding anticipated dates for similar analyses in the PD-L1 \geq 1% subgroup are [redacted] and [redacted], respectively.

6.24 At the time of the [REDACTED] data cutoff, the number of deaths among all randomised subjects was [REDACTED]. Results for the first interim analysis of OS for the ITT population and for the PD-L1 ≥ 1% subgroup are presented in Table 7. The corresponding KM curves are presented in Figure 3 and [REDACTED] Figure 4.

Table 7: CM274 - Overall survival – Interim analysis (ITT and PD-L1 positive populations)

	ITT population		PD-L1 ≥ 1% subgroup	
	NIVO (N=[REDACTED])	PBO (N=[REDACTED])	NIVO (N=[REDACTED])	PBO (N=[REDACTED])
Events, n (%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Median overall survival (95% CI), months ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HR ^b (99.8% CI)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
p-value	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Overall survival rates^a				
At 9 months, % (95% CI)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
At 12 months, % (95% CI)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Source: Tables 12-5, p55-59 of the Round 2 clinical evaluation report for nivolumab (Submission PM-2021-02518-1-4)
 CI = confidence interval; HR = hazard ratio; NE = not estimable (not reached); ITT = intention to treat (all randomised patients); NIVO = nivolumab; PBO = placebo; PD-L1 = programmed cell death ligand 1

Notes: ITT: Median follow-up time was 24.44 months for the nivolumab arm and 22.51 months for the placebo arm.

PD-L1 ≥ 1% subgroup: Median follow-up time was [REDACTED] months for the nivolumab arm and [REDACTED] months for the placebo arm

^aBased on Kaplan-Meier estimates

^bNivolumab versus placebo

^cLog-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, PD-L1 status (≥ 1% versus < 1% / indeterminate). Boundary for statistical significance p-value <0.00196

Figure 3: CM274 – Kaplan-Meier plots for overall survival – Interim analysis (ITT)

[REDACTED] Source: Figure 10, p58 of the Round 2 TGA clinical evaluation report for nivolumab (Submission PM-2021-02518-1-4)
 CI = confidence interval; ITT = intention to treat; NA = not available (not reached).

Figure 4: CM274 – Kaplan-Meier plots for overall survival – Interim analysis (PD-L1 ≥ 1% subgroup)

[REDACTED] Source: Figure 11, p59 of the Round 2 TGA clinical evaluation report for nivolumab (Submission PM-2021-02518-1-4).
 CI = confidence interval; NA = not available (not reached); PD-L1 = programmed cell death ligand 1.

6.25 The median duration of follow-up in the ITT population was 24.4 months for the nivolumab arm and 22.5 months for the placebo arm. Nivolumab was associated with a [REDACTED]% reduction of the hazard of death which was not statistically significant (HR [REDACTED], [REDACTED]%, CI: [REDACTED], [REDACTED]; p=[REDACTED]). The median OS was [REDACTED] months (95% CI: [REDACTED], not reached) with nivolumab versus [REDACTED] months (95% CI: [REDACTED], not reached) with placebo. There was an [REDACTED] of the KM curves favouring [REDACTED]. The OS data remain immature as at data cutoff noting that the KM curves appear to [REDACTED] at around the [REDACTED] month time point.

6.26 The median duration of follow-up in the PD-L1 ≥ 1% subgroup was 25.5 months for the nivolumab arm and 22.4 months for the placebo arm. Nivolumab was associated with a [REDACTED] of the hazard of death although this reduction in hazard [REDACTED] (HR [REDACTED], [REDACTED]%, CI: [REDACTED], [REDACTED]; p=[REDACTED]). The median OS was [REDACTED].

6.27 There were limited OS data provided for PD-L1 <1% subgroup. The OS HR for nivolumab compared with placebo [REDACTED] (HR [REDACTED], 95% CI: [REDACTED], [REDACTED]) noting that this subgroup comprised approximately [REDACTED] ([REDACTED]%) of the ITT population.

6.28 Table 8 summarises results for the secondary/exploratory outcomes of non-urothelial tract recurrence-free survival (NUTRFS) and distant metastasis-free survival (DMFS) in the CM274 ITT population. No results were presented for the PD-L1 positive subgroup.

Table 8: Secondary and exploratory efficacy results for NUTRFS and DMFS – ITT population

Efficacy parameters	NIVO (N=353)	PBO (N=356)
NUTRFS		
Events, n (%)	165 (46.7%)	199 (55.9%)
Median duration NUTRFS (95% CI), months ^a	26.0 (19.5, 41.1)	13.7 (8.4, 20.0)
HR ^b (95% CI)	0.71 (0.58, 0.88)	
Rate at 6 months ^a , %	77.1%	62.9%
Rate at 12 months ^a , %	65.8%	50.6%
DMFS		
Events, n (%)	135 (38.2%)	160 (44.9%)
Median DMFS (95% CI), months ^a	41.1 (26.0, NE)	29.2 (15.2, NE)
HR ^b (95% CI)	0.73 (0.58, 0.92)	

Source: Table 28, p73 of the submission.

CI = confidence interval; DMFS = distant metastasis-free survival; HR = hazard ratio; NIVO = nivolumab; NE = not estimable; NUTRFS = non-urothelial tract recurrence-free survival; PBO = placebo; ITT = intention to treat.

Notes: NUTRFS was defined as the time between the date of randomisation and the date of first local recurrence outside the urothelial tract, distant recurrence, or death, whichever occurred first

DMFS was defined as the time between the date of randomisation and the date of first distant recurrence (non-local) or date of death (from any cause).

^a Based on KM estimates.

^b Stratified Cox proportional hazard model. HR is NIVO over PBO.

- 6.29 Nivolumab was associated with a statistically significant 29% reduction in the hazard of non-urothelial tract recurrence or death compared with placebo (HR 0.71, 95% CI: 0.58, 0.88). The median duration of NUTRFS was 26.0 months in the nivolumab arm and 13.7 months in the placebo arm. The NUTRFS event free rate at 12 months was higher in the nivolumab arm (65.8%) than in the placebo arm (50.6%).
- 6.30 Nivolumab was also associated with a statistically significant 27% reduction in the hazard of distant metastases or death compared with placebo (HR 0.73, 95% CI: 0.58, 0.92). The median duration of DMFS was longer in the nivolumab arm than in the placebo arm (41.1 months versus 29.2 months, respectively).
- 6.31 HRQoL data from the CM274 trial were based on the July 2020 data cutoff. The median duration of follow-up was 20.9 months in the nivolumab arm and 19.5 months in the placebo arm (ITT population). The percentage of patients that completed the EORTC QLQ^{§§§}-C30 in both treatment arms was $\geq 85\%$ during the treatment period (through 49 weeks) and $\geq 75\%$ in the follow-up period (Visits 1 and 2). At baseline, mean EORTC QLQ-C30 summary scores for all domains were comparable between treatment arms. The PBAC noted that changes from baseline in the EORTC QLQ-C30 global health status score and the EQ-5D-3L visual analogue scale score over time indicated that there was no meaningful difference in deterioration in quality of life between patients who received nivolumab and those who received placebo. No statistical tests were performed on change from baseline scores between treatment arms.
- 6.32 It is recognised that EORTC QLQ-C30 and EQ-5D scales have become international standards for HRQoL measurement. However, these tools have several limitations in the context of novel therapies such as immune checkpoint inhibitors. For example, the QLQ-C30 includes questions pertaining to nausea and vomiting, with few other cancer therapy-related questions represented in the tool. These are frequent issues associated with cytotoxic chemotherapy (not a comparator in the CM274 trial) and immune checkpoint inhibitors are associated with a unique set of immune mediated adverse reactions. The PBAC considered the HRQoL results do not reflect the higher

^{§§§} European Organisation for Research and Treatment of Cancer quality of life questionnaire

rate of toxicity in the nivolumab treatment arm compared to placebo in the CM274 trial (see Benefits/Harms Section).

Comparative harms

6.33 Table 9 summarises the results of safety outcomes for the CM274 trial during the on-treatment period (July 2020 data cutoff, median duration of follow-up 20.9 months and 19.5 months in the nivolumab and placebo arms, respectively; median duration of treatment 8.8 months and 8.2 months in the nivolumab and placebo arms, respectively). The safety results should be interpreted with caution given that in the CM274 double-blinded trial, the placebo arm did not include active anti-cancer treatment during the on-treatment period.

Table 9: CM274 - Overview of clinical AEs across treatment groups – safety evaluable population

AE Category	NIVO (N=351) n (%)	PBO (N=348) n (%)	Risk ratio [95% CI]	Risk difference [95% CI]
All causality				
AE (any grade)	347 (98.9%)	332 (95.4%)	1.04 [1.01, 1.06]	0.03 [0.01, 0.06]
Severe AE (grade 3 or 4)	148 (42.2%)	122 (35.1%)	1.20 [1.00, 1.45]	0.07 [-0.00, 0.14]
SAE (any grade)	104 (29.6%)	105 (30.2%)	0.98 [0.78, 1.23]	-0.01 [-0.07, 0.06]
Severe SAE (grade 3 or 4)	81 (23.1%)	73 (21.0%)	1.10 [0.83, 1.45]	0.02 [-0.04, 0.08]
Discontinuation of study treatment due to				
AEs (any grade)	64 (18.2%)	32 (9.2%)	1.98 [1.33, 2.95]	0.09 [0.04, 0.14]
Severe AEs (grade 3 or 4)	39 (11.1%)	21 (6.0%)	1.84 [1.11, 3.06]	0.05 [0.01, 0.09]
Death	95 (27.1%)	107 (30.7%)	0.88 [0.70, 1.11]	-0.04 [-0.10, 0.03]
Study drug related				
AE (any grade)	272 (77.5%)	193 (55.5%)	1.40 [1.25, 1.56]	0.22 [0.15, 0.29]
Severe AE (grade 3 or 4)	63 (17.9%)	25 (7.2%)	2.50 [1.61, 3.88]	0.11 [0.06, 0.16]
SAE (any grade)	32 (9.1%)	7 (2.0%)	4.53 [2.03, 10.13]	0.07 [0.04, 0.10]
Severe SAE (grade 3 or 4)	26 (7.4%)	6 (1.7%)	4.30 [1.79, 10.31]	0.06 [0.03, 0.09]
Discontinuation of study treatment due to				
AEs (any grade)	45 (12.8%)	7 (2.0%)	6.37 [2.91, 13.94]	0.11 [0.07, 0.15]
Severe AEs (grade 3 or 4)	25 (7.1%)	5 (1.4%)	4.96 [1.92, 12.80]	0.06 [0.03, 0.09]
Death	3 (0.9%) ^a	0 (0.0%)	6.94 [0.36, 33.87]	0.01 [-0.00, 0.02]

Source: Table 29, p80 of the submission

AE = adverse event; CI = confidence interval; SAE = serious adverse event; NIVO = nivolumab; PBO = placebo.

Notes: Results in **bold** indicate statistical significance ($p < 0.05$).

The risk ratios (RR) and risk differences (RD) were for nivolumab versus placebo. $RR > 1$ and $RD > 0$ favour placebo over nivolumab.

^aTwo treatment-related deaths due to pneumonitis and one treatment-related death due to bowel perforation occurred in the nivolumab arm.

6.34 Adverse events (AEs) were reported in almost all patients in both treatment arms (98.9% in nivolumab arm, 95.4% in placebo arm). The risk ratios (RRs) and risk differences (RDs) were statistically significant favouring placebo over nivolumab for the following AEs:

- Study drug-related serious AE (SAE), any grade (RR 4.53 [95% CI: 2.03, 10.13])
- Study drug-related severe Grade 3-4 AE (RR 2.50 [95% CI: 1.61, 3.88]);
- Study drug-related Grade 3-4 SAE (RR 4.30 [95% CI: 1.79, 10.31]); and
- Discontinuation of study treatment due to a Grade 3-4 severe AE (RR 4.96 [95% CI: 1.92, 12.80]).

6.35 Two (0.6%) treatment-related deaths due to pneumonitis and one (0.3%) treatment-related death due to bowel perforation occurred in the nivolumab group. The most common drug related AEs reported in the nivolumab arm were pruritus (23.1%), fatigue (17.4%), diarrhoea (16.8%), and rash (15.1%). The most common SAEs were

urinary tract infection (2.6%), malignant neoplasm progression (2.3%), intestinal obstruction (1.4%), acute kidney injury (1.4%) and sepsis (1.1%).

- 6.36 AEs of special interest (AESIs) included demyelination, encephalitis, Guillain-Barré syndrome, myasthenia, myocarditis, myositis, pancreatitis, rhabdomyolysis, graft versus host disease and uveitis. Overall, AESIs were reported in 2.3% of patients in the nivolumab arm and 1.1% subjects in the placebo arm (p87, Round 2 CER for nivolumab, Submission PM-2021-02518-1-4).
- 6.37 Overall, no new safety issues were identified from the CM274 trial. The safety profile of nivolumab monotherapy was consistent with previously documented safety data.

Benefits/harms

- 6.38 A summary of the comparative benefits and harms for nivolumab versus placebo is presented in Table 10.

Table 10: Summary of the comparative benefits and harms for nivolumab versus placebo (proxy for watchful waiting)

Benefits						
	Nivolumab N=353	Placebo N=356	Absolute difference	HR (95% CI) [p-value]		
DFS (median duration of follow-up: Nivolumab 24.4 months, Placebo 22.5 months) - ITT						
Recurrence or death, n (%)	175 (49.6)	213 (59.8)		0.70 (0.57, 0.85) p=0.0005 ^a		
Median DFS, months (95% CI)	22.0 (17.7, 36.9)	10.9 (8.3, 14.0)	11.1 months			
DFS rate at 30 months, % (95% CI)	44.9% (39.0, 50.7)	35.5% (30.1, 40.9)	9.4%			
Overall survival interim analysis (median duration of follow-up: Nivolumab [redacted] months, Placebo [redacted] months)						
Death, n (%)	[redacted]	[redacted]		HR (99.8% CI)		
Median OS, months (95% CI)	[redacted]	[redacted]				
Alive at 12 months, % (95% CI)	[redacted]	[redacted]				
Harms (median duration of treatment: Nivolumab 8.8 months, Placebo 8.2 months) – Safety evaluable population						
Event	Nivolumab n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Nivolumab	Placebo	
Grade 3-4 study drug related severe SAE	26/351	6/348	4.30 (1.79, 10.31)	7.4	1.7	0.06 (0.03, 0.09)
Any grade pruritus	81/351	40/348	2.01 (1.42, 2.84)	23.1	11.5	0.12 (0.06, 0.17)

Source: Table 29–30, pp80–1 of the submission

AE = adverse event; DFS = disease-free survival; HR = hazard ratio; ITT = intention to treat; NE = not estimable (not reached); OS = overall survival; SAE = serious adverse event.

Notes: HR for DFS and OS were for nivolumab versus placebo. HR <1 favour nivolumab over placebo. Risk ratios (RR) and risk differences (RD) in safety outcomes were for nivolumab versus placebo. RRs > 1 and RDs > 0 favour placebo over nivolumab.

Safety based on safety evaluable population.

^aLog-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, PD-L1 status (≥ 1% versus < 1% / indeterminate).

- 6.39 On the basis of the direct evidence presented in the submission, for every 100 patients treated with nivolumab in comparison with placebo (median duration of follow-up: Nivolumab 24.4 months, Placebo 22.5 months):

- Approximately 9 additional patients will remain free of disease recurrence or death at 30 months.
- Approximately 6 additional patients will experience a life-threatening or severe serious adverse event.
- Approximately 12 additional patients will experience pruritus (any possible grade).

The impact on OS is unknown.

Clinical claim

6.40 Based on the direct comparison in the CM274 trial, the submission described nivolumab as superior in terms of effectiveness and inferior in terms of safety compared to placebo (as a proxy for watchful waiting). The evaluation suggested the following issues should be considered when interpreting the effectiveness results from the CM274 trial:

- Only an interim analysis of OS was available and the OS data remain immature. With a median follow-up of 24 months in the nivolumab arm and 23 months in the placebo arm, approximately |% and |% of events had occurred in the nivolumab and placebo arms, respectively. Longer-term data are required to determine whether the observed improvement in DFS translates into a clinically meaningful OS benefit. The PSCR stated that reducing the risk of cancer recurrence is a meaningful and important clinical benefit, particularly among patients at high risk of recurrence. The PSCR argued that the DFS outcome can be considered a standalone measure of clinical benefit and as it is reported earlier than OS it is not confounded by subsequent cancer therapies. The ESC considered that while DFS is a hard endpoint for adjuvant chemotherapy, its use as an endpoint to predict OS for adjuvant immunotherapy is not as clear. The ESC considered this is particularly the case in cancers where there may be a subgroup of patients who have disease recurrence but may still enter a cure phase after subsequent therapy in the metastatic setting. In addition, the ESC noted that the OS data were immature and considered its relevance to the Australian setting uncertain given the subsequent use of immunotherapies in the CM274 trial did not reflect current Australian clinical practice. It was maintained in the pre-PBAC response that DFS is a patient-relevant and clinically meaningful endpoint that is well supported by Australian clinicians. The pre-PBAC response also argued that, consistent with Australian clinical practice, a large proportion (57%) of patients in the placebo arm of the CM274 trial who received immunotherapy did so as a second-line therapy. Further, the pre-PBAC response argued that use of immunotherapy in the first-line setting, prior to chemotherapy in the placebo arm (not reflective of Australian practice), may mean that the clinical benefit of adjuvant nivolumab compared with placebo is conservative compared to the Australian setting.
- There was no clear benefit observed in patients who had not received prior neoadjuvant cisplatin-based chemotherapy. In clinical practice, patients who have not received prior neoadjuvant platinum-based chemotherapy would usually be offered, if eligible, adjuvant platinum-based chemotherapy. No comparative evidence for adjuvant nivolumab versus adjuvant chemotherapy was presented in the submission, with the submission noting that there was high uncertainty with an indirect comparison. The PSCR highlighted that CM274 was not powered to identify statistically significant differences in treatment effect in subgroups beyond patients with PD-L1 expression $\geq 1\%$. Despite this, the ESC considered that the trial data strongly suggested there is less treatment benefit associated with adjuvant nivolumab for patients who have not received prior neoadjuvant cisplatin-based chemotherapy compared with patients who had received

neoadjuvant cisplatin-based chemotherapy and considered this to be a primary clinical issue of the submission. It was maintained in the pre-PBAC response that CM274 was not powered to compare subgroups based on prior use of neoadjuvant chemotherapy. It was also stated that this subgroup analysis may be subject to confounding, as there were more placebo arm subjects with N+ nodal status in the prior neoadjuvant chemotherapy group than in the no prior neoadjuvant chemotherapy group, which is associated with poorer prognosis compared with N- nodal status.

- Notwithstanding the small sample size and exploratory nature of the subgroup analysis, there was no clear benefit observed in patients with upper urothelial tumours (renal pelvis and ureter), with the DFS HR point estimates indicating that nivolumab could be potentially inferior compared with placebo. In clinical practice, UTUC patients who have not received prior neoadjuvant platinum-based chemotherapy would usually be offered, if eligible, adjuvant platinum-based chemotherapy. Importantly, evidence from the POUT trial**** demonstrated that in UTUC patients, post-nephroureterectomy (either pT2–T4 pN0–N3 M0 or pT any N1–3 M0), adjuvant platinum-based chemotherapy substantially improved DFS (HR 0.45, 95% CI: 0.30, 0.68; p=0.0001) and metastasis free survival (HR 0.48, 95% CI: 0.31, 0.74; p=0.0007) compared with surveillance. The ESC considered the urothelial tumour subgroup analysis uncertain due to small patient numbers and agreed with the PSCR that it cannot be reliably concluded that patients with UTUC tumours are different from the whole study population.

6.41 The ESC considered the claim of inferior comparative safety to placebo was reasonable and adequately supported by the data.

6.42 The PBAC considered that the claim of superior comparative effectiveness was uncertain but likely reasonable if restricted to patients who had received prior neoadjuvant platinum-based chemotherapy.

6.43 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.44 The submission presented a stepped economic evaluation comparing adjuvant nivolumab treatment versus placebo in patients with high-risk MIUC who have undergone radical surgery, based on the CM274 trial clinical trial, with modelled extrapolation and Australian costing. A cost-effectiveness analysis and a cost-utility analysis were presented measuring outcomes in terms of life years (LYs) gained and quality-adjusted life years (QALYs) gained, respectively. The key components of the economic evaluation are presented in Table 11.

**** Birtle A et al (2020). Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *The Lancet*, Issue 10232, 18–24 April 2020, pp1268-1277.

Table 11: Summary of model structure, key inputs and rationale

Component	Description
Type of analysis	Cost-effective analysis and cost-utility analysis
Outcomes	Life years gained, quality-adjusted life years
Time horizon	20 years in the model base case vs. median follow-up of 24.4 months in the nivolumab arm and 22.5 months in the placebo arm in the key trial (CM274).
Methods used to generate results	Markov model
Health states	Pre-recurrence, recurrence and death
Cycle length	4 weekly for one year; 3-monthly thereafter
Transition probabilities and extrapolation method	<p>Pre-recurrence to recurrence: Individual patient data for DFS from the CM274 trial until 29.5 months (median follow-up estimated by reverse Kaplan-Meier method) followed by independent generalised gamma extrapolation of DFS applied to individual treatment arms was used to determine the transitions from pre-recurrence to post-recurrence for five years, then a 100% cure rate was applied.</p> <p>Recurrence to death: As the submission did not provide OS data, transitions from post-recurrence to death were assumed to be independent of treatment and informed in the base case by two Phase III randomised controlled trials investigating first-line metastatic treatment of urothelial carcinoma. The monthly hazard rate was assumed to be identical between the two treatment arms and constant over the entire time horizon.</p> <p>Pre-recurrence to death: Transitions from pre-recurrence to death were calculated using background population mortality data. For the first two years, this background death rate was elevated (by a factor of 1.5) as per calculations using DFS.</p>
Utilities	<p>EQ-5D data collected in the CM274 trial were used to inform the utility values applied to each health state.</p> <p>Utilities: Pre-recurrence: 0.83 Recurrence: 0.734</p> <p>The economic model incorporated adverse event-related disutility values obtained from the literature.</p>

Source: Compiled during the evaluation, based on Table 38, pp101 and Section 3 of the submission.
CM274 = CheckMate 274; DFS = disease free survival; OS = overall survival

- 6.45 The economic model assumed a 20-year time horizon. A lifetime time horizon allows capturing all differences between adjuvant nivolumab and watchful waiting with regard to costs and outcomes incurred throughout the disease course of MIUC after complete resection. However, the trial data did not provide a reliable basis for a long-term extrapolation. A lifetime time horizon adds uncertainty to the incremental cost-effectiveness ratio (ICER) result, particularly given the uncertainties regarding the extrapolation function, the cure assumption, and the estimation of the transition probabilities from the recurrence health state to death. Approximately 81% of the incremental QALYs between the treatment arms accumulated during the extrapolation period; whilst minimal increase in incremental costs was modelled during this period. The time horizon is a key driver of the model favouring nivolumab, and the ESC felt that a shorter time horizon was appropriate given the clinical data.
- 6.46 The model included three health states – recurrence-free, recurrence and death. The crude structure of the submission’s economic model combined locoregional recurrence and locally advanced/metastatic recurrence into one health state, despite

the heterogeneity (in terms of both costs and health outcomes) of these settings. This was inappropriate and could not reflect the disease course of high-risk MIUC after radical surgery and adjuvant therapy with nivolumab or watchful waiting. The PBAC has previously had a concern that a single recurrent disease health state was unlikely to reflect the outcomes of patients treated with adjuvant nivolumab in melanoma (Nivolumab PSD, July 2018). Following this the sponsor updated the model with the disease recurrence health state split into two health states, patients with locoregional recurrence and patients with distant metastatic recurrence (Nivolumab PSD, March 2019). The PSCR stated that based on CM274 trial data similar rates of locoregional recurrence and distant recurrence were observed for patients in both arms of the trial and therefore nivolumab does not appear to alter the nature of recurrence. The ESC agreed with the evaluation that it was not appropriate for the economic model to combine locoregional recurrence and locally advanced/metastatic recurrence into one health state. It considered that one health state did not provide the granularity required to accurately reflect the differences in disease progression seen in MIUC patients. The ESC considered that the health state did not account for less severe recurrences (i.e. local recurrence), and also a small probability of cure in the metastatic setting as a result of treatment with subsequent therapies. It was argued in the pre-PBAC response that the inclusion of separate health states for locoregional recurrence and locally advanced/metastatic recurrence is not expected to be a key model driver. The sponsor stated that there was also limited data to inform the transition probabilities as these events from the CM274 trial remain immature.

- 6.47 The probability of remaining in the pre-recurrence health state was derived from the DFS KM estimates from the CM274 trial for the respective treatment arms until the median trial follow-up as estimated using reverse KM method (29.5 months). The CM274 trial was an appropriate source for estimation of DFS. The PBAC guidelines (version 5.0) recommend use of trial-data until the time point where the trial data is no longer reliable due to the small number of patients at risk. At the extrapolation time point used in the model (29.5 months), more than 60 patients in each treatment arm were at risk for a DFS event (Month 30: n=72 in the nivolumab arm and n=67 in the placebo arm, Figure 1), which suggested 29.5 months may have been too early as a time point for extrapolation. There was still a reasonable number of patients at risk at Month 42 (n=31 in the nivolumab arm and n=32 in the placebo arm); thereafter, this number dropped quickly due to censoring. The ESC noted the PSCR argument that a data truncation point of 29.5 months was reasonable as 20% of the cohort remained at risk. However, the ESC considered that given the size of the trial there remained a sufficient number at risk (10% of the cohort) for a truncation point of 42 months to be considered appropriate. The ESC noted the use of a later truncation point increased the ICER (see Table 16). The pre-PBAC response argued that the increase in the ICER estimate when using the KM curves from 39 months to 42 months reflects the uncertainty in the curves given that only two DFS events occurred during this time period. The sponsor was of the view that use of the KM curves is reasonable to 39 months but is unreliable thereafter.
- 6.48 From 29.5 months to 5 years, a patient's probability of remaining in the DFS health state was determined by extrapolating the patient level data from CM274 using parametric distribution functions. The submission extrapolated DFS data using an

independent generalised gamma function for both treatment arms in the base case. Based on visual inspection and goodness of fit statistics, Gompertz distribution was considered the best fit, however the relatively flat tail was deemed clinically implausible by the submission. The submission's explanation to dismiss the Gompertz function is inconsistent with the submission's assumption that a 'cure' is claimed where no disease recurrence is modelled after 5 years – i.e. that flattening off is assumed to occur. Overall, the selection of extrapolation function is highly uncertain and the submission's rationale for not selecting the Gompertz in each arm is unconvincing given a subsequent cure assumption is applied at 5 years; such an assumption would be implicit without external manipulation of the extrapolation if these statistically best-fitting curves were used. Alternative functions are tested in the sensitivity analyses. The method of extrapolation was a key driver of the model. The PSCR acknowledged that the independent Gompertz extrapolation reported the lowest AIC and BIC for placebo and the lowest BIC for nivolumab. However, it was considered in the PSCR that the Gompertz DFS curve flattens too soon (30 to 36 months) compared to the DFS rates reported in Sternberg (2015). The ESC considered the independently fit Gompertz curves reasonable. It was argued by the sponsor in the pre-PBAC response that the Gompertz curves were inappropriate given that after year 8 in the economic model the probability of recurrence is much lower for the Gompertz curve than the probability of mortality in the general population.

- 6.49 The model applied a cure assumption at 5 years, i.e. the transition probability from the pre-recurrence state to the post-recurrence state is '0' at the end of 5 years and the only way of transition is from pre-recurrence to death based on background mortality. The time point for cure and the 100% cure rate was based on clinical expert opinion from a pre-Advisory Board survey. The extended period without disease recurrence, considered to be a cure by clinicians, varied from 3 years to 10 years. For the time after 5 year cure point, some clinicians noted there was always a risk of recurrence. The PSCR stated that the assumption of cure is well supported by clinical evidence, expert opinion, and treatment guidelines. The ESC considered a cure assumption at 5 years reasonable as it was of the view that MIUC is an aggressive disease where most recurrences would likely occur within a 5 year timeframe. The PBAC agreed with the ESC that a cure assumption at 5 years was likely reasonable for MIUC.
- 6.50 Due to the immaturity of the OS data from the trial, the transition probability from recurrence to death was estimated based on the weighted health outcome (median OS) from two Phase III trials of first-line treatment for locally advanced or metastatic urothelial carcinoma. The same transition probability was used in both treatment arms and the monthly hazard rate remained constant over the entire time horizon. The setting of the external trials was limited to advanced and metastatic urothelial cancer. The costs and the health outcomes associated with other post-recurrence events, e.g. locoregional recurrence, were not taken into account in the model. The ESC agreed with the evaluation that patients from the selected trials of first-line treatment for locally advanced or metastatic urothelial carcinoma were likely to have more advanced disease compared with the proposed patient population and therefore considered the probability of death post-recurrence was likely to have been overestimated. The ESC also considered a time constant probability not appropriate.

The pre-PBAC response stated that the time constant extrapolation for post-recurrence survival was appropriate and did not deviate from observed data (difference of -0.14 to 0.49 months over a five-year period).




- 6.51 The subsequent treatment considered in the post-recurrence health state of the model was first-line platinum-based chemotherapy in both arms. However, further lines of therapies would differ between the two treatment arms and thus the outcomes, given the availability of PD-(L)1 inhibitors for treatment of advanced or metastatic MIUC following first-line chemotherapy in the comparator watchful waiting arm. The health outcomes and costs associated with later-line use of PD-(L)1 inhibitors were not appropriately considered in the economic model. It was not appropriate to assume identical transition probabilities from post-recurrence to death between the two treatment arms. The ESC noted that the direction of the ICER from relaxing this assumption is uncertain. The pre-PBAC response argued that the inclusion of costs and outcomes associated with the use of pembrolizumab in the second-line metastatic setting would lead to a reduction in the ICER.
- 6.52 Figure 5 presents the DFS and OS estimates from the CM274 trial and from the economic model. A comparison of the trial-based OS data and the modelled OS curves indicated that the modelled OS estimates were  than the trial-based data in both treatment arms. The gap between the OS curves for the two treatment groups was  in the economic model. However, it was noted that there were applicability issues regarding the use of subsequent anti-cancer therapies in CM274, especially the sequential use of immunotherapy in the nivolumab arm of CM274 (around 18% of patients with disease recurrence). It was acknowledged in the PSCR that post-recurrence survival may have been underestimated in the submission. The PSCR noted that when applying a 0.6x multiplier to the Australian population death rates the observed and modelled OS are similar over the first three years.

Figure 5: Comparison of modelled and trial based DFS and OS estimates

 Source: Figure constructed during the evaluation, based on Figure 10, p58 of the Round 2 TGA clinical evaluation report for nivolumab (Submission PM-2021-02518-1-4) and the 'Attachment 12 - Nivolumab Adjuvant MIUC Economic Evaluation' Excel workbook.
DFS = disease free survival; NIVO = nivolumab; OS = overall survival; WW = watchful waiting

- 6.53 The transition probability from pre-recurrence to death was based on the general population mortality sourced from Australian Bureau of Statistics (ABS) Life Tables (2017-2019). In the base case, background mortality for patients before recurrence has been adjusted by a standard mortality ratio (SMR) of 1.5 for the initial period of two years. The method used to determine the SMR appeared reasonable and the finding of increased mortality risk is consistent with other studies that identify significantly increased non bladder-cancer mortality in bladder cancer patients, potentially with higher SMR estimates in the short-term^{****}. However the submission does not justify stopping the multiplier after the initial 2 years; the literature suggests that bladder cancer patients have an ongoing increased risk of death due to other causes even in the long-term, therefore it is suggested that the SMR continue to be applied throughout the entire time horizon of the model or at least to the cure

^{****} Kong J, Diao X, Diao F, Fan X, Zheng J, Yan D, et al. Causes of death in long-term bladder cancer survivors: A population-based study. *Asia-Pacific Journal of Clinical Oncology*. 2019;15(5):e167-e74.
Zhai M, Tang C, Li M, Chen X, Jin Y, Ying X, et al. Short-term mortality risks among patients with non-metastatic bladder cancer. *BMC Cancer*. 2020 2020/11/25;20(1):1148.

assumption. The ESC agreed with the evaluation that the point at which the 1.5x mortality multiplier was withdrawn was not well justified and noted that the ICER was impacted by varying this assumption.

6.54 The health state utilities were estimated based on the EQ-5D data collected in the CM274 trial. The EQ-5D health utility scores were derived based on the Australia value set^{****}. Utilities in each health state did not vary across treatment arms. To take into account the inferior safety profile of nivolumab, the submission incorporated AE-related disutility values obtained from the literature. The submission noted that 50% to 60% of participants were excluded by week 48, which was primarily due to disease recurrence and treatment toxicity. It was also assumed that HRQoL does not differ substantially between drug toxicity and disease recurrence, the group difference is unlikely to be affected by missing data. The validity of this assumption is uncertain. Additionally, in CM274 trial, the HRQoL data were collected only twice after treatment discontinuation, i.e. to a maximum of 3 months after disease recurrence. The deteriorating HRQoL of the patients over the entire post-recurrence health state were not fully captured in the trial. Overall, the utilities for both health state, especially the post-recurrence, could have been overestimated in the model. A sensitivity analysis was performed during the evaluation by reducing the utility for pre-recurrence health state by 0.05 (arbitrary value) and for post-recurrence health state by 0.1 (arbitrary value). The result showed that the model was not sensitive to these utility inputs.

6.55 A summary of the key drivers of the model is given in Table 12.

Table 12: Key drivers of the model

Description	Method/Value	Impact Base case: \$ ¹ /QALY
Time horizon	Model adopted a 20-year time horizon.	Moderate, favoured nivolumab. Time horizon of 10 years and 15 years, increased the ICER to \$ ² /QALY and \$ ¹ /QALY, respectively.
Extrapolation time point	29.5 months	Moderate, favoured nivolumab Trial data extrapolated from 42 months, the ICER increased to \$ ¹ /QALY.
Extrapolation of DFS	Generalised gamma in both arms	Moderate, favoured nivolumab Changing the method of extrapolation to Gompertz in both arms, increased the ICER to \$ ³ /QALY.
Application of cure assumption	5 years	Moderate, favoured nivolumab Applying the cure assumption at 7 years and 10 years increased the ICER to \$ ¹ /QALY and \$ ³ /QALY.

Source: Compiled during the evaluation, based on Section 3.9 of the submission and the sensitivity analyses performed during the evaluation
DFS = disease-free survival; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year;

The redacted values correspond to the following ranges:

¹\$35,000 to < \$45,000

²\$55,000 to < \$75,000

³\$45,000 to < \$55,000

6.56 The results of the stepped economic evaluation presented in the submission are summarised in Table 13.

**** Viney R, Norman R, King MT, Cronin P, Street DJ, Knox S, et al. Time trade-off derived EQ-5D weights for Australia. *Value Health*. 2011 Sep-Oct;14(6):928-36.

Table 13: Results of the stepped economic evaluation

Costs			Health outcomes			ICER (\$)
NIVO (\$)	WW (\$)	Incremental (\$)	NIVO	WW	Incremental	
Step 1 - Comparative study data^c						Recurrence or death avoided
			48.16% ^b	57.30% ^b	9.14% ^b	█ ¹ █ ^{a2}
Step 2 - Comparative study data^c						LYG
			2.017	1.862	0.155	█ ³
Step 3 - Study data transformed to QALY outcome^c						QALY
			1.627	1.486	0.141	█ ³
Step 4 - Study data transformed to QALYs & extrapolated to 20 year time horizon						QALY
			4.410	3.679	0.731	█ ⁴

Source: Table 65, p141 of the submission

ICER = incremental cost-effectiveness ratio; NIVO = nivolumab; WW = watchful waiting

^a It is unclear how the ICER of \$555,000 to < \$655,000 per recurrence or death avoided was calculated in the submission. Based on the given incremental cost (\$█) and incremental outcome (9.14% recurrence or death avoided), the ICER was estimated to be \$255,000 to < \$355,000 per recurrence or death avoided.

^b Includes recurrence and death

^c Time horizon set to median follow-up of trial of approximately 30 months (2.5 years)

The redacted values correspond to the following ranges:

¹\$555,000 to < \$655,000

²\$255,000 to < \$355,000

³\$155,000 to < \$255,000

⁴\$35,000 to < \$45,000

6.57 The extension of the time horizon to 20 years (Step 4) had a significant impact on the ICER, increasing the incremental QALYs gained from 0.141 to 0.731. Meanwhile, the extension of the time horizon only resulted in a slight increase in incremental costs from \$█ to \$█, which was primarily due to the differential disease management costs accumulated between the two treatment arms. The ICER decreased from \$155,000 to < \$255,000/QALY gained in the trial period to \$35,000 to < \$45,000/QALY gained at 20-year time horizon.

6.58 The evaluation identified a number of issues with the approaches and assumptions in the model. The results of a respecified model are presented in Table 14. This base case:

- utilised the best-fitting Gompertz functions to independently extrapolate each arm;
- used more of the clinical trial data (truncated at 42 months);
- did not add a 5 year cure assumption (this has been captured in the Gompertz curve);
- maintained the increased SMR for all-cause mortality throughout the model;
- increased the disutility for adverse events; and
- corrected the chemotherapy pricing.

Table 14: Results of the stepped economic evaluation with respecifications

Costs			Health outcomes			ICER (\$)
Nivo (\$)	WW (\$)	Incremental (\$)	Nivo	WW	Incremental	
Step 1 - Comparative study data^b						Recurrence avoided
			48.16% ^a	57.30% ^a	9.14% ^a	1
Step 2 - Comparative study data^b						LYG
			2.017	1.862	0.155	2
Step 3 - Study data transformed to QALY outcome^b						QALY
			1.622	1.485	0.137	2
Step 4 - Study data transformed to QALYs & extrapolated to 20 year time horizon						QALY
			4.616	4.083	0.533	3

Source: Constructed during the evaluation based on, Table 65, p141 of the submission and respecified model assumptions

ICER = incremental cost-effectiveness ratio; Nivo = nivolumab; WW = watchful waiting

^a Includes recurrence and death

^b Time horizon set to median follow-up of trial of approximately 30 months (2.5 years)

The redacted values correspond to the following ranges:

¹\$255,000 to < \$355,000

²\$155,000 to < \$255,000

³\$55,000 to < \$75,000

6.59 Table 15 summarises the number of recurrences and deaths avoided in the economic model over the 20-year time horizon together with a comparison of the number of events avoided in the CM274 trial.

Table 15: Average events per patient in the trial versus the economic model

	CheckMate274 (median follow-up: 24.4 months in the nivolumab arm and 22.5 months in the watchful waiting arm)			Economic model (time horizon of 20 years)		
	Nivolumab	Watchful waiting	Difference	Nivolumab	Watchful waiting	Difference
Recurrence events	% ^a	% ^a	%	65.9% ^b	73.6% ^c	-7.7%
Deaths	% ^d	% ^d	%	82.3% ^e	86.4% ^f	-4.1%
Life years (undiscounted)	1.751 ^g	1.478 ^h	0.273	7.264 ⁱ	5.989 ^j	1.275

Source: Table compiled during the evaluation, based on the 'Attachment 12 - Nivolumab Adjuvant MIUC Economic Evaluation' Excel workbook.

^a Calculated by subtracting pre-recurrence deaths from number of patients with a DFS event in each arm (153/353 in nivolumab arm and 193/356 in watchful waiting arm)

^b Sum Z101:Z129 in 'Model' tab of 'Attachment 12 - Nivolumab Adjuvant MIUC Economic Evaluation' Excel workbook.

^c Sum AR101:AR129 in 'Model' tab of 'Attachment 12 - Nivolumab Adjuvant MIUC Economic Evaluation' Excel workbook.

^d

^e Sum AA101:AA189 in 'Model' tab of 'Attachment 12 - Nivolumab Adjuvant MIUC Economic Evaluation' Excel workbook.

^f Sum AS101:AS189 in 'Model' tab of 'Attachment 12 - Nivolumab Adjuvant MIUC Economic Evaluation' Excel workbook.

^g Value in cell G8 after Setting Cell E35 = 2.033 and Cell E36 = 0% in 'Model' tab of Attachment 12 - Nivolumab Adjuvant MIUC Economic Evaluation' Excel workbook.

^h Value in cell H8 after Setting Cell E35 = 1.875 and Cell E36 = 0% in 'Model' tab of Attachment 12 - Nivolumab Adjuvant MIUC Economic Evaluation' Excel workbook.

ⁱ Value in cell G8 after Setting Cell E35 = 20 and Cell E36 = 0% in 'Model' tab of Attachment 12 - Nivolumab Adjuvant MIUC Economic Evaluation' Excel workbook.

^j Value in cell H8 after Setting Cell E35 = 20 and Cell E36 = 0% in 'Model' tab of Attachment 12 - Nivolumab Adjuvant MIUC Economic Evaluation' Excel workbook.

6.60 The proportion of patients experiencing recurrence in the nivolumab arm increased from 43.3% in the CM274 trial to 65.9% by the end of the 5 years in the model. The corresponding recurrence results in the comparator arm were 54.2% in the trial versus 73.6% in the economic model. Though the modelled time horizon was 20 years, recurrence events were considered to occur only until 5 years, thereafter a 100% cure

rate (i.e. no recurrence) was assumed. The absolute difference between the two treatment arms was smaller at the end of 5 years than in the trial (-1% vs. -7.7%), because over time a higher proportion of patients transitioned from pre-recurrence to recurrence health state in the nivolumab arm, compared with the watchful waiting arm, due to a higher proportion of patient at risk (i.e. remaining in the pre-recurrence state). The proportion of patients who died increased from 1% to 82.3% in the nivolumab arm and from 1% to 86.4% in the watchful waiting arm during the extrapolation period. A comparison of the trial results and the model results suggested that the main benefit of adjuvant nivolumab relative to watchful waiting over the 20-year time horizon was delaying and preventing the occurrence of disease recurrence, and thus death events. The mean LYs gained increased from 0.273 during the trial period to an extrapolated 1.275 at Year 20.

6.61 The base case (20 year time horizon) estimated (undiscounted) for every patient treated with nivolumab:

- A primary drug cost of \$1; and
- 1.275 LYs gained.

For every 1,000 patients treated:

- Nivolumab drug cost of \$1;
- 77 recurrence events avoided;
- 70 more people cured (at year 5);
- 41 deaths avoided; and
- 1,275 LYs gained.

6.62 Results of univariate and multivariate sensitivity analyses specified by the submission and additional analyses conducted during the evaluation are presented in Figure 6 and Table 16.

Figure 6: Change in ICER over time horizon



Source: Figure constructed during the evaluation, based on 'Attachment 12 – Nivolumab Adjuvant MIUC Economic Evaluation' Excel workbook.

ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

6.63 Examining the relationship between the ICER and the time horizon of the model reveal that the ICER dropped substantially until levelling out at around 4 years at about \$115,000 to < \$135,000/QALY gained. Then the ICER decreased gradually to less than \$45,000 to < \$55,000/QALY gained at around 12 years before approaching \$35,000 to < \$45,000/QALY gained at year 20.

Table 16: Results of sensitivity analyses

	Variable	Base case	Sensitivity analysis	Cost/QALY (\$)	% change from base case
Base case					
SA.1	Time horizon	20 years	10 years	1	43%
SA.2			15 years	1	13%
SA.3	Extrapolation of nivolumab DFS	Generalised gamma	Log-logistic	3	27%
SA.4			Gompertz	4	-35%
SA.5			Log-normal	3	13%
SA.6	Extrapolation of placebo DFS	Generalised gamma	Log-logistic	4	-15%
SA.7			Gompertz	5	290%
SA.8			Log-normal	1	-12%
SA.9 ^a	Extrapolation of nivolumab and placebo DFS	Generalised gamma	Gompertz (both arms)	3	37%
SA.10 ^a	Point of extrapolation of DFS	Median time to follow-up (30 months)	42 months	1	13%
SA.11 ^a	Cure assumption	5 years	3 years	4	-17%
SA.12 ^a			10 years	3	16%
SA.13 ^a			20 years (no cure)	3	19%
SA.14 ^a	Utilities ^a	Pre-recurrence: 0.83 Post-recurrence: 0.734	Pre-recurrence: 0.78 Post-recurrence: 0.634	1	6%
SA.15 ^a	Background mortality multiplier (x1.5)	Limited to first 2 years	Entire time horizon (20 years)	1	5%
SA.16 ^a	Convergence of curves	No convergence	At 15 Years ^b	6	93%
SA.9+SA.13 (Gompertz + No cure) ^a				2	47%
SA.9+SA.10+SA.13 (Gompertz + 42 months extrapolation +No cure) ^a				2	44%
SA.9+SA.10+SA.13 +SA.15 (Gompertz + 42 months extrapolation + No cure + background mortality multiplier (x1.5) for 20 years) ^a				2	41%

Source: Table 72, p146 of the submission and additional analyses conducted during the evaluation.

DFS = disease-free survival; QALY = quality-adjusted life year

^a Sensitivity analyses performed during the evaluation.

^b DFS and OS curves of both arms were made to converge by changing the point of cure to 15 years and by increasing the transition probability of pre-recurrence to recurrence and recurrence to death by approximately 1.3 and 1.5 times respectively in the nivolumab arm from year 4.

The redacted values correspond to the following ranges:

¹\$35,000 to < \$45,000

²\$55,000 to < \$75,000

³\$45,000 to < \$55,000

⁴\$25,000 to < \$35,000

⁵\$155,000 to < \$255,000

⁶\$75,000 to < \$95,000

6.64 The ICER was found to be moderately sensitive to time horizon, choice of parametric function for extrapolation of DFS, time point of extrapolation of DFS and cure assumption. If Gompertz parametric function was used to extrapolate DFS in both treatment arms from 42 months, no cure was considered and the background mortality multiplier of 1.5 was applied to the entire time horizon of 20 years, the ICER would increase by 41% to \$55,000 to < \$75,000 /QALY gained (base case: \$35,000 to < \$45,000/QALY gained).

6.65 The ESC considered that the respecified base case outlined in Table 14 is likely to be a more accurate representation of the true ICER than the base case provided in the submission. The ESC advised it would be appropriate for the respecified base case

assumptions to be used when consideration is given to providing a model with a more granular recurrence state.

Drug cost/patient/course

Table 17: Drug cost per patient for nivolumab as adjuvant therapy

	Trial dose and duration	Model	Financial estimates
Mean dose per infusion	240mg Q2W	480mg Q4W	240mg Q2W (10%) 480mg Q4W (90%)
Mean duration	16.9 cycles ^a	8.5 cycles ^a	240mg Q2W: 16.9 cycles ^a 480mg Q4W: 8.5 cycles ^a
Cost/patient/cycle	\$ ^b	\$ ^b	240mg Q2W: \$ ^b 480mg Q4W: \$ ^b
Cost/patient/course	\$	\$	\$

Source: Table constructed during the evaluation, based on Table 21, p59 of the submission; on 'Attachment 12 – Nivolumab Adjuvant MIUC Economic Evaluation'; Table 74 of the submission

Q2W = every 2 weeks; Q4W = every 4 weeks

^a Based on cumulative mean dose from CheckMate 274 trial

^b Assuming 33.35% of the nivolumab scripts will be dispensed in a public hospital setting, and 66.65% in a private hospital setting.

Estimated PBS usage & financial implications

6.66 This submission was not considered by DUSC.

6.67 A summary of the data sources and parameter values used to estimate the utilisation and financial implications associated with the listing of adjuvant nivolumab is provided in Table 18.

Table 18: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source and Comment
Eligible population		
Incident cases of (T1-T4)	3,699 in Year 1 (2023) to 3,964 in Year 6 (2028)	AIHW cancer incidence, ABS data on the growth rate of Australian population. While the AIHW was an appropriate data source for incidence, the evaluation considered the growth rate of the Australian general population cannot reflect the growth rate of incident patients with bladder, ureter or renal pelvis cancer.
Incident cases of bladder, ureter or renal pelvis cancer (Ta and Tis)	4,689 in year 1 (2023) to 5,001 in year 6 (2028)	AIHW cancer incidence data, with an annual growth rate of 1.3%, Reynolds et al 2021 The evaluation considered this was reasonable, apart from the annual growth rate.
Proportion of urothelial carcinoma	In bladder cancer: 89% In ureter and renal pelvis cancer: 93.5%	Personal communication of the sponsor with AIHW The evaluation considered the estimates appeared to be comparable with the literature
Proportion diagnosed with MIUC (T2-T4a, N+, M0)	53.47% of T1 to T4 population	Reynolds et al 2021 The evaluation considered this was a reasonable data source
Proportion of patients with NMIUC	Proportion T1: 46.53% of T1 to T4 population Ta and Tis population: 55.9% of all urothelial cancer cases in Australia	AIHW, Reynolds et al 2021 The evaluation considered this was reasonable
Proportion diagnosed with NMIUC who progress to MIUC	13%	BLADDA registry ^a Consistent with the estimate reported in the literature
Proportion of MIUC with radical resection	64.67%	BLADDA registry ^a Consistent with the estimate reported in literature and clinician opinion

Data	Value	Source and Comment
Proportion of patients with WHO performance status of 0 or 1	98%	BLADDA registry ^a The evaluation considered this was reasonable
Risk of recurrence after radical surgery	50%	Pre-Advisory Board survey The evaluation considered this was a likely underestimate (see paragraph 6.69 for details).
Treatment utilisation		
Uptake rate of nivolumab	% across Years 1 to 6	Pre-Advisory Board survey Uncertain, not adequately justified.
Treatment duration of nivolumab	Q2W: 16.90, Q4W: 8.48 (based on Q2W)	CM274 trial The evaluation considered this was appropriate
Relative use of nivolumab Q2W vs Q4W	Q2W: 10%, Q4W: 90%	Previous PBAC advice (Nivolumab PSD, March 2019) The PBAC considered that it was reasonable to assume that the majority of patients would be prescribed the 480 mg Q4W dosing regimen if available.
Drug cost		
Nivolumab effective cost per administration (weighted)	240mg: \$ 480 mg: \$	Proposed effective price Appropriate
MBS fee		
Administration of antineoplastic agent	\$112.40	MBS item 13950 Appropriate
Others		
Proportion of PBS vs. RPBS	PBS: 96.84%, RPBS: 3.16%	Based on existing PBS Item statistics from January to December 2021 for nivolumab PBS listings for adjuvant melanoma. Reasonable
Patient co-payment	PBS: \$26.69 RPBS: \$6.77	

Source: Table 75, p175 of the submission

ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; MIUC = muscle invasive urothelial carcinoma; NMIUC = non-muscle invasive urothelial carcinoma; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = public summary document; Q2W = two-weekly dosing; Q4W = four-weekly dosing; RPBS = Repatriation Pharmaceutical Benefits Scheme

^aTran, B. (2022). BLADDA – Bladder and Urothelial Cancer Data and Biobank, Data Report. References folder (Part 3) accompanying the submission.

6.68 The size of the eligible population was estimated using the Australian Institute Health and Welfare (AIHW) data on the number of incident cases of bladder cancer in Year 2021 and the number of incident cases of cancer of other urinary organs (ureter cancer and renal pelvis cancer) in Year 2016. An annual rate of 1.3% was applied, based on the Australian population growth rate from the Australian Bureau of Statistics. The growth rate of the general population may not reflect the growth rate of cancer incidence. The average annual growth rate of incident patients diagnosed with bladder, ureter or renal pelvis cancer was estimated to be 2.1%, based on the AIHW data in 2010-2021 (actual incidence data from 2010–2017 and projected data from 2018–2021), higher than the 1.3% rate used in the financial analysis. Therefore, the submission could have underestimated the number of the eligible patients and, thus, the cost of the treatment with nivolumab. It was stated in the PSCR that more recent (2016–2017) data was received from the AIHW for the incidence of cancer of the bladder, renal pelvis and ureter for urothelial cell carcinoma histological types. Based on these data, the growth rate of incident patients in 2016 was 1.02% and 0.99% in 2017. The PSCR considered these data an accurate estimate of growth and noted that it is similar to the 1.3% used in the financial analysis. The ESC considered the 3-year incidence data may be of insufficient duration for estimating the growth of incidence patients, and advised the estimates within the evaluation were more

reliable for decision-making. The sponsor maintained that the Australian general population growth and the updated AIHW data (2016–2017) were more accurate sources to estimate the annual growth in incidence than the actual/projected AIHW data (2010–2017) suggested in the evaluation and supported by the ESC (pre-PBAC response).

- 6.69 The submission assumed that 50% of patients with T2-T4 disease (i.e. MIUC) will recur following radical resection. The submission stated that this estimate was based on the feedback from a Genitourinary Advisory Board meeting with medical oncologists and urologists held by the sponsor. High risk was not defined when the clinicians in the Advisory Board provided the estimate. The financial analysis effectively assumed that only 50% of the patients who are classified as Stage T2-T4 (MIUC) before surgery will have pathological Stage ypT2-pT4a or ypN+ (where neoadjuvant chemotherapy has been given) or pT3-pT4a or pN+ (where no neoadjuvant chemotherapy has been given) disease based on pathological staging of radical surgery tissue, as per the definition of high risk in the proposed PBS listing. It was stated in the PSCR that the percentage estimate for recurrence was also supported by a retrospective review of radical cystectomy reporting 46% of patients developed a recurrence, which aligns with the 50% estimate applied in the submission. Despite this, the ESC considered that this assumption was not reasonable and results in uncertainty of the number of eligible patients and the cost of nivolumab adjuvant treatment. It was maintained by the sponsor in the pre-PBAC response that Australian clinicians are the best placed to inform the proportion of patients that are at high risk of recurrence.
- 6.70 The rate of uptake of treatment with nivolumab (██████%) used in the financial analysis was based on the expert opinion from the Genitourinary Advisory Board, with no further justification. It is unknown whether the uptake of adjuvant nivolumab estimated by the 12 medical oncologists and urologists in the Advisory Board could be realised in Australian clinical practice following the proposed listing of nivolumab. The sponsor stated in the PSCR that the uptake rate assumed in the submission was supported by an additional follow-up consultation with urologists. The ESC agreed with the evaluation that the uptake rate assumed in the submission may be underestimated. It was maintained by the sponsor in the pre-PBAC response that Australian clinicians are the best placed to inform the uptake rate of nivolumab.
- 6.71 The submission assumed that the PBS listing of adjuvant nivolumab will not result in a change in the use of other PBS medicines as the main comparator is ‘watch and wait’ surveillance; and nivolumab as adjuvant therapy is expected to substitute no active treatment. However, it should be noted that the availability of nivolumab has the following impacts:
- Given the inferior safety of nivolumab in comparison with no active treatment, patients receiving nivolumab may require medicines for management of treatment-related AEs.
 - Meeting minutes of clinician consultation provided as part of the submission suggested that the introduction of adjuvant nivolumab will likely cause 10% increase in the use of neoadjuvant chemotherapy.
 - It was envisaged that some patients treated with nivolumab as adjuvant therapy would otherwise receive adjuvant chemotherapy without the listing of nivolumab.

- It is likely that PD-1/PD-L1 inhibitors (such as pembrolizumab) may be prescribed in the later lines of therapy after recurrence in current clinical practice (before the listing of adjuvant nivolumab), but not in patient treated with nivolumab in the adjuvant setting.

6.72 The submission assumed that the only MBS item likely to be affected by the PBS listing of nivolumab is item 13950, which is associated with administration of adjuvant nivolumab therapy. Eighty percent of the MBS schedule fee (\$98.92 = \$112.4 x 80%) was applied to all patients who receive intravenous infusion of nivolumab. Given the toxicity profile of nivolumab, patients receiving nivolumab might require additional clinician visits and investigational services (e.g. renal function test, hepatic function test etc) for monitoring of drug toxicities and, thus, incur additional costs to the MBS. The submission did not include these costs.

6.73 At year 6, the estimated number of patients was 476 and the net cost to the PBS/RPBS would be \$10 million to < \$20 million.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed ^a	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated financial implications of nivolumab						
Cost to PBS/RPBS less copayments (\$)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments	\$0	\$0	\$0	\$0	\$0	\$0
Net financial implications						
Net cost to PBS/RPBS (\$)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to MBS (\$)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Net cost to PBS/RPBS/MBS (\$)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³

Source: Compiled during the evaluation, based on 'Attachment 13 – Nivolumab Adjuvant MIUC Utilisation and Cost Model' Excel workbook

MBS = Medicare Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a The mean number of scripts was 16.96 for the 240 mg Q2W dosing regimen (10% of patients) and 8.48 for the 480 mg Q4W dosing regimen (90% of patients).

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$10 million to < \$20 million

⁴ \$0 to < \$10 million

Quality Use of Medicines

6.74 The submission stated that the sponsor is committed to supporting the safe and effective use of nivolumab in Australia. Given the adverse effect profile of immunology agents, the sponsor has established an extensive quality use of medicines (QUM) approach to optimise the potential benefits of treatment with nivolumab, while minimising the potential risks of this medicine for Australian patients. The submission's QUM activities include physician education, immune-oncology preceptorship, peer-to-peer support, nursing and pharmacy in-services, a risk

management plan, educational materials and tools, and guidance on monitoring and treating immune related adverse reactions.

- 6.75 The PBAC considered the potential that UTUC patients eligible for effective adjuvant platinum-based chemotherapy may forgo clinical benefit if treated with nivolumab instead was a QUM issue.

Financial Management – Risk Sharing Arrangements

- 6.76 An RSA was not proposed by the submission. It is expected that the proposed listing of nivolumab as adjuvant therapy would affect the extent of use of other PD-1 inhibitors for treatment of advanced or metastatic urothelial carcinoma but this has not been estimated by the submission. The sponsor stated in the PSCR and pre-PBAC response that it is willing to enter a RSA related to expenditure to provide additional certainty to government.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of nivolumab for adjuvant treatment of patients who have 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. The PBAC considered that, while a small improvement in disease free survival (DFS) was demonstrated with nivolumab compared to placebo in the overall trial population, there was a strong suggestion that a benefit was observed only in patients who had received prior neoadjuvant platinum-based chemotherapy. The PBAC also noted the impact of nivolumab as adjuvant treatment on overall survival (OS) was unknown. The PBAC considered that the incremental cost-effectiveness ratio (ICER) was uncertain and likely underestimated, and that revisions to the structure and inputs for the economic model are required.
- 7.2 The PBAC noted the input from health care professionals and organisations highlighting the impact of MIUC and its treatments on health-related quality of life (HRQoL) combined with the effects of a generally poor prognosis and fear of recurrence. The PBAC noted support for nivolumab for this indication from the Medical Oncology Group of Australia (MOGA). The PBAC considered there was a moderate clinical need for more effective therapies for this indication, noting that neoadjuvant chemotherapy can be effective and immunotherapy is available in the metastatic setting.
- 7.3 The PBAC considered the comparator of watchful waiting appropriate. However, the PBAC agreed with the ESC that adjuvant platinum-based chemotherapy was a relevant comparator in eligible patients who have not received neoadjuvant chemotherapy.
- 7.4 The primary clinical evidence supporting the clinical claim was the CM274 clinical trial (N=709) comparing adjuvant nivolumab with placebo in subjects with high risk invasive urothelial carcinoma. The PBAC noted a statistically significant reduction in the hazard of recurrence or death favouring nivolumab (hazard ratio (HR) = 0.70 (95% CI: 0.57, 0.85)) with no difference in HRQoL. However, the PBAC considered that no clear improvement in DFS was observed with nivolumab over placebo in patients who had not received prior neoadjuvant cisplatin-based chemotherapy (prior use: HR =

0.52 (95% CI: 0.39, 0.71); no prior use: HR = 0.90 (95% CI: 0.68, 1.18)). The PBAC also considered that the magnitude of treatment benefit for patients with an upper tract urothelial cancer (UTUC) was highly uncertain. Nonetheless, the PBAC agreed with the ESC that given the small sample size it cannot be reliably concluded that patients with UTUC tumours are different from the whole study population.

- 7.5 The PBAC noted that only an interim analysis of OS data was available and that the data remained immature. In addition, the PBAC agreed with the ESC that the relevance of the OS data to the Australian setting was uncertain given the subsequent use of immunotherapies in the CM274. The PBAC noted that among patients who experienced recurrence, approximately 18% (28/153) and 44% (85/193) of patients received immunotherapy in the nivolumab and placebo arms, respectively. Sequential use of immunotherapy as observed in the nivolumab arm is not indicated in Australia and the PBAC considered the proportion of use in the placebo arm is also unlikely to reflect current Australian clinical practice. The PBAC noted the Pre-Sub-Committee Response (PSCR) argument that the DFS outcome can be considered a standalone measure of clinical benefit that is not confounded by subsequent cancer therapies. The PBAC considered that the relationship between DFS and OS observed for adjuvant chemotherapy does not necessarily hold for adjuvant immunotherapy, and further the relationship will be impacted by subsequent therapy, including immunotherapy, received in the metastatic setting for patients who have disease recurrence. As such, the PBAC considered that longer-term data are required to determine whether the observed improvement in DFS translates into a clinically meaningful OS benefit.
- 7.6 Overall, the PBAC considered nivolumab provided a small benefit in DFS compared with placebo for patients with MIUC, but the impact on OS was unknown. In addition, the PBAC considered there was a strong suggestion that the DFS benefit was observed only in patients who had received prior neoadjuvant cisplatin-based chemotherapy. As such, the PBAC considered the claim of superior comparative effectiveness was uncertain but likely reasonable for patients who have received prior neoadjuvant platinum-based chemotherapy.
- 7.7 The PBAC considered that a claim of inferior safety was reasonable. The PBAC noted that there was an approximate 11% increase in grade 3 or 4 serious adverse events associated with nivolumab compared with placebo in the CM274 trial. However, the PBAC considered the overall safety associated with nivolumab treatment in the adjuvant setting was acceptable.
- 7.8 The PBAC noted the issues with the economic model that had been raised by the evaluation and the ESC, including:
- The time horizon of the base case in the economic model was 20 years. It was considered that the trial data did not provide a reliable basis for a long-term extrapolation and it was considered that a shorter time horizon would be more appropriate.
 - Locoregional recurrence and locally advanced/metastatic recurrence were combined into one health state in the economic model, despite their heterogeneity. The ESC considered the one health state did not account for less severe recurrences (i.e. local recurrence), and also a small probability of cure in the metastatic setting as a result of treatment with subsequent therapies. The

PBAC noted that both distant and local recurrences were evident in CM274 trial participants (see Table 6).

- The economic model did not use the best fitting DFS extrapolations (independent Gompertz) and applied early data truncations to the Kaplan-Meier (KM) data.

The PBAC noted that the submission base case ICER was sensitive to time horizon, the time point of data truncation, extrapolation of DFS, and the application of a cure assumption.

- 7.9 The PBAC noted that the evaluation presented a respecified base case that increased the ICER from \$35,000 to < \$45,000/QALY gained to \$55,000 to < \$75,000 /QALY gained (see paragraph 6.58). The PBAC noted the respecified base case addressed some of the concerns raised by ESC outlined in paragraph 7.8. However, the PBAC considered the respecified base case ICER to be unacceptably high for the adjuvant therapy setting and advised it remained optimistic. The PBAC considered that the uncertainties associated with the economic model may be managed with the inclusion of more conservative assumptions regarding time horizon in the respecified base case and a model structure that accommodated separate health states for locoregional recurrence and locally advanced/metastatic recurrence. The PBAC considered that an ICER of up to \$30,000/QALY gained would be consistent with previous PBAC decisions in the adjuvant therapy setting.
- 7.10 The PBAC considered the financial estimates presented in the submission were high and potentially underestimated. The PBAC noted the concerns raised during the evaluation and by the ESC relating to incident growth, the percentage of patients at high-risk of recurrence, and the assumed uptake rate. The PBAC considered a risk sharing arrangement (RSA) would likely be required with the recommendation to limit treatment to patients who had received prior neoadjuvant chemotherapy to manage the risk of use outside this population.
- 7.11 The PBAC considered a resubmission for nivolumab should address the following issues:
- Restrict use to patients who have received prior neoadjuvant platinum-based chemotherapy (see paragraph 7.6), and revise the economic model and financial estimates accordingly;
 - Provide updated OS data from the second interim analysis of the CM274 clinical trial (see paragraph 6.23);
 - Revise the structure of the economic model to include a more granular recurrence state and address the uncertainties raised during the evaluation and by the ESC (see paragraph 7.8);
 - Address the uncertainties raised during the evaluation and by the ESC regarding the financial forecasts
 - An outline of an RSA to manage the risk of use in patients who have not received prior neoadjuvant platinum-based chemotherapy.
- 7.12 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Bristol-Myers Squibb Australia looks forward to continuing to work with the PBAC and the Department of Health to provide access to nivolumab for the adjuvant treatment of patients who have undergone radical resection of muscle invasive urothelial carcinoma and are at high risk of recurrence.