7.04 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. The Standard re-entry submission (herein referred to as resubmission) requested a Section 100 (Efficient Funding of Chemotherapy Program [EFC]) Authority Required (Telephone/Online) listing for the adjuvant treatment of high-risk muscle invasive urothelial carcinoma (MIUC). The target population in the requested listing proposed in the resubmission is now restricted to patients who have received prior neoadjuvant platinum-based chemotherapy (NAC) (unless patients have a contraindication/ intolerance to NAC) compared to that in the previous submission which was regardless of prior use of NAC.
	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 resubmission**

|  |  |
| --- | --- |
| Component | Description |
| Population | Patients with muscle invasive urothelial carcinoma (MIUC) who have undergone radical resection surgery and are at high risk of recurrence, and who have received prior neoadjuvant platinum-based chemotherapy (NAC). Patients who have a contraindication/intolerance to NAC are eligible for nivolumab. |
| Intervention | Nivolumab |
| Comparator | Watch and wait surveillance |
| Outcomes | Disease-free survival (DFS), non-urothelial tract recurrence-free survival (NUTRFS), disease-specific survival (DSS), distant metastasis-free survival (DMFS), health-related quality of life (HRQoL), safety and tolerability |
| Clinical claim | Nivolumab has superior efficacy and inferior safety compared to watch and wait surveillance |

Source: Table 1, p14 of the resubmission.

Blue shading indicates information previously seen by the PBAC.

1. Background

Registration status

* 1. Nivolumab was registered on the Australian Register of Therapeutic Goods on 18July 2022 as monotherapy for the adjuvant treatment of patients with MIUC who are at high-risk of recurrence after undergoing radical resection of MIUC.
	2. In the recently published Australian Public Assessment Report (AusPAR)[[1]](#footnote-2), the Advisory Committee on Medicines (ACM) was of the view that the population eligible for nivolumab should be consistent with the population assessed for efficacy in the clinical study where higher risk was defined as either: 1) ypT2-ypT4a or ypN+, for patients who received neoadjuvant cisplatin; or 2) pT3-pT4a or pN+, for patients who did not receive neoadjuvant cisplatin and who also either were ineligible for or refused adjuvant cisplatin[[2]](#footnote-3),[[3]](#footnote-4). The ACM advised that it would be appropriate to define high risk by staging criteria in the Product Information (PI).
	3. The ACM noted that regarding adjuvant treatment, overall survival (OS) data are critical, as within this setting the clinician’s aim is often to increase OS. The ACM was supportive of the mature OS data being provided to the TGA once available and agreed with having this as a condition of registration. The ACM reiterated that while disease-free survival (DFS) is a relevant outcome, oncologists often refer to OS data and long-term toxicity when determining benefit-risk profiles (AusPAR).
	4. The ACM noted that there is not yet strong data in support of the use of nivolumab within upper urothelial tract cancers (renal pelvis and ureter) and agreed that this should be noted within the PI. Overall, noting that much of the submitted data were early data, the ACM was of the view that the indication should remain as proposed and additional details be included within the PI at this time.
	5. The ACM advised that while it appears there is greater benefit with higher programmed cell death ligand 1 (PD-L1) expression, there is also evidence in the data to date of a broader benefit regardless of PD-L1 expression.
	6. 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 | 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 ≥ 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. | As adjuvant treatment of adult patients with MIUC with PD-L1 expression ≥1%, who are at high-risk of recurrence based on pathologic evidence after undergoing complete (R0) radical resection of MIUC and who received neo-adjuvant cisplatin chemotherapy or have not received neo-adjuvant cisplatin chemotherapy and are not eligible for or refused adjuvant cisplatin chemotherapy. |
| Approval date | 19 August 2021 | 1 April 2022 | 27 June 2022 | 28 February 2022 |

Source: Table 3, pp20-21 of the resubmission.

EMA = European Medicines Agency; MIUC = muscle invasive urothelial carcinoma; PD-L1 = programmed cell death ligand 1; USA = United States of America

Previous PBAC consideration

* 1. Table 3 summarises the key matters of concern from the previous PBAC consideration and how the resubmission addressed those concerns.

Table 3: **Summary of key matters of concern**

| Component | Matter of concern in previous submission(Nivolumab PSD, July 2022 PBAC meeting) | How the resubmission addresses it |
| --- | --- | --- |
| Target population and clinical effectiveness | The PBAC noted the impact of nivolumab as adjuvant treatment on overall survival (OS) was unknown (para 7.1) and that a resubmission should provide updated OS data from the CM274 clinical trial (para 7.11).  | Not addressed. The resubmission noted that OS data remain immature at the September 2022 data cutoff and therefore did not present any OS results.  |
| No clear disease-free survival (DFS) benefit was observed with nivolumab over placebo in patients who had not received neoadjuvant cisplatin-based chemotherapy (para 7.4) and that a resubmission should restrict use to patients who have received prior neoadjuvant platinum-based chemotherapy (para 7.11). | Addressed. Restriction amended to reflect PBAC comments. However, the requested restriction allows patients who are contraindicated or intolerant to neoadjuvant platinum-based chemotherapy to access nivolumab. Efficacy remains unclear in these patients. |
| The magnitude of treatment benefit for patients with an upper tract urothelial cancer (UTUC) was highly uncertain. However, 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 (para 7.4). | Not addressed. As per the CM274 protocol, the number of subjects enrolled with UTUC was capped at 20%. Data remain unreliable for this subgroup. |
| Subsequent therapies in CM274 | Subsequent anti-cancer therapies in CM274 does not appear to reflect the expected use of subsequent anti-cancer treatment in Australian clinical practice. Sequential use of immunotherapy 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 programmed cell death (ligand) 1 (PD-(L)1) inhibitor (para 6.15). | Not addressed. The impact and applicability of subsequent therapies post-recurrence from the CM274 trial remain uncertain. |
| Safety  | The PBAC considered the health-related quality of life (HRQoL) results do not reflect the higher rate of toxicity in the nivolumab treatment arm compared to placebo in the CM274 trial (para 6.32). | Not addressed. HRQoL data in CM274 do not reflect the higher toxicity profile of nivolumab compared to placebo from the CM274 data. |
| Economic evaluation | The PBAC considered that use should be restricted only to patients who have received prior neoadjuvant platinum-based chemotherapy (para 7.11) | Addressed. Key inputs used in the model have been restricted to this subgroup of the CM274 trial |
|  | The PBAC considered that the trial data did not provide a reliable basis for long-term extrapolation to 20 years and that a shorter time horizon would be more appropriate (para 7.8). | Unchanged as the resubmission argued that as the model assumed that some patients achieve a cure, an extended time horizon is required to capture the outcomes of these long-term survivors. Modelled outcomes however remain based on a number of assumptions and are associated with a high degree of uncertainty. |
|  | The PBAC requested that the structure of the economic model be revised to include a more granular recurrence state, as locoregional recurrence and locally advanced/metastatic recurrence had been combined into one health state, despite their heterogeneity (para 7.8 and 7.11). 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 (para 7.8). | Addressed. The resubmission separated the post-recurrence health state into locoregional and distant recurrence and applied differing costs and outcomes to each health state. The resubmission included modelling of a cure in patients with both locoregional and distant recurrence (based on expert opinion). |
|  | The PBAC noted that the economic model did not use the best fitting DFS extrapolations (independent Gompertz) (para 7.8).  | While the resubmission used a Gompertz model (on the basis that this was previously the best fit to the CM274 ITT data), this was not the best fitting function to DFS data from the prior-NAC subgroup treated with nivolumab |
|  | The PBAC noted early truncations to the Kaplan-Meier (KM) data used in the model (para 7.8). At the chosen truncation time point (29.5 months) a substantial number of patients remained at risk of a DFS event. This suggested that more of the observed data could have been reliably used (para 6.47). | Kaplan-Meier data was used until 54 months, at which time 20 patients (12.8%) in the NIVO arm and 11 patients (7.0%) in the watchful waiting arm remain at risk. While this was reasonable for the NIVO arm, given the small numbers remaining at risk, the data used in the watchful waiting arm are likely unreliable at this point |
| Financial estimates/Management | The ESC noted that the approach used to estimate the number of incident cases of (T1-T4), based on general population growth rates, could be an underestimate (para 6.68) | Unchanged. This was not reasonable given that the AIHW have published projections to 2031. |
|  | Risk of recurrence after radical surgery: 50% Pre-Advisory Board survey. 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 (para 6.69).  | Unchanged as the resubmission claimed that in the absence of literature to support otherwise, this was the best source to inform this estimate. This remains for PBAC consideration. |
|  | Uptake rate of NIVO: 57%The ESC noted that the uptake rate assumed in the submission may be underestimated (para 6.70). | A higher uptake rate (90%) was applied. This was made on the basis that the intent would be to treat with nivolumab. As an increase in NAC use was assumed following nivolumab listing, it is therefore unclear whether patients treated with nivolumab in practice would reflect those patients in the prior-NAC subgroup of CM274. |
|  | 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 (para 7.10).The PBAC considered a resubmission for nivolumab should address or provide an outline of an RSA to manage the risk of use in patients who have not received prior neoadjuvant platinum-based chemotherapy (para 7.11). | Not addressed. No RSA was proposed in the resubmission. Of note, the requested restriction allows patients who are contraindicated or intolerant to neoadjuvant platinum-based chemotherapy to access nivolumab. |

Source: Nivolumab Public Summary Document (PSD), July 2022 PBAC meeting; Nivolumab resubmission.

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

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| MEDICINAL PRODUCTForm | PBS item code | Maximum amount | Dispensed price for maximum amount | №.of Rpts |
| NIVOLUMAB Injection | NEW (Public)NEW (Private)MP | 480 mg | Published (Private Hospital)$9,731.26aPublished (Public Hospital)$9,557.05aEffective (Private Hospital)$||||aEffective (Public Hospital)$||||a | 5 |
| Available brands |
| Opdivo(nivolumab 40 mg/4 mL injection, 4 mL vial) |
| Opdivo(nivolumab 100 mg/10 mL injection, 10 mL vial) |
|  |
| Restriction Summary New 1 / Treatment of Concept: New 1.1: Authority Required |
|  | Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals |
| Prescriber type: [x] Medical Practitioners |
| Restriction Type: [x] Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues) |
|  | **Episodicity:** [blank] |
| **Severity:** [blank] |
| **Condition:** ~~[blank]~~Urothelial carcinoma |
|  | **Indication:** Urothelial carcinoma |
|  |  |
|  | **Clinical criteria:** |
|  | The treatment must be for each of: (i) adjuvant therapy that ~~initiates~~ *is/was* initiated 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 for this condition. |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have received prior platinum containing neoadjuvant chemotherapy; or |
|  | Patient must have a contraindication/intolerance to platinum containing neoadjuvant chemotherapy |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have/have had, at the time of initiating treatment with this drug, a WHO performance status no higher than 1 |
|  |  |
|  | **Treatment criteria:** |
|  | Patient must be undergoing treatment with a dosing regimen as set out in the drug's approved Australian Product Information |
|  | **AND** |
|  | **Treatment criteria:** |
|  | *Patient must be undergoing treatment that does not occur beyond the following, whichever comes first: (i) the first instance of disease progression/recurrence, (ii) 12 months in total for this condition from the first administered dose; mark any remaining repeat prescriptions with the words 'cancelled' where (i)/(ii) has occurred.*~~Patient must not be undergoing PBS-subsidised treatment with this drug where this prescription extends treatment beyond whichever comes first: (i) 12 months from treatment initiation, irrespective of whether initial treatment was PBS-subsidised/non-PBS-subsidised, (ii) disease recurrence despite treatment with this drug; annotate any remaining repeat prescriptions with the word ‘cancelled’ where this occurs.~~ |
|  |  |
|  | ***Administrative Advice:****Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.* |
|  | **Administrative Advice:** An increase in repeat prescription*s* ~~numbers~~, up to a value of 11, may only be sought where the prescribed dosing is *240 mg administered* fortnightly. |

a Applying the July 2023 Efficient Funding of Chemotherapy mark-ups and fees, the published dispensed prices for nivolumab would be $9,734.47 (Private) and $9,558.60 (Public) and the effective dispensed prices for nivolumab would be $| | (Private) and $| | (Public).

* 1. The resubmission proposed a special pricing arrangement (SPA) with an effective Public hospital dispensed price for maximum amount (DPMA) of $| | (published $9,558.60) and an effective Private hospital DPMA of $| | (published $9,734.47), using the July 2023 Efficient Funding of Chemotherapy (EFC) fees and mark-ups. The proposed effective DPMAs requested in the resubmission have more than doubled the prices proposed in the previous submission ($| | [public] and $| | [private]).
	2. The resubmission requested that nivolumab be restricted to patients who have had prior NAC or who are contraindicated/intolerant to NAC. Subgroup analysis from the CM274 trial indicated there is no clear DFS benefit for patients with no prior use of NAC (September 2022 cut-off: Prior NAC use: HR = 0.54 [95% CI: 0.41, 0.72]; No prior NAC use: HR = 0.88 [95% CI: 0.68, 1.14]; February 2021 cut-off: (Prior NAC use: HR = 0.52 [95% CI: 0.39, 0.71]; No prior NAC use: HR = 0.90 [95% CI: 0.68, 1.18]). In the July 2022 consideration of nivolumab for MIUC, the PBAC noted that a resubmission for nivolumab should restrict use to patients who have received prior NAC (paragraph 7.11, nivolumab Public Summary Document (PSD), July 2022 PBAC meeting). The ESC noted that the Pre-Sub-Committee response (PSCR) argued that the inclusion of patients who are contraindicated or intolerant to NAC in the proposed restriction is consistent with clinician feedback, ensures patient equity of access, and promotes clinical autonomy for treating physicians. The ESC considered a patient must have received at least one dose of NAC to be determined intolerant to this treatment and hence would meet the ‘must have received prior NAC criterion’. However, the ESC considered the inclusion of a criterion regarding patients who are contraindicated or intolerant to NAC would substantially increase the likelihood of use in a patient population with no proven treatment benefit and advised it should be removed from the proposed restriction. The pre-PBAC response stated that clinician feedback highlighted the potential inequitable consequence of restricting access to the prior NAC treated population and proposed the removal of the word ‘intolerance’ in the criterion.
	3. In July 2022, the PBAC 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 (paragraph 3.6, nivolumab PSD, July 2022 PBAC meeting)
	4. The resubmission noted that consistent with advice proposed by the Secretariat for the previous submission (paragraph 3.4, nivolumab PSD, July 2022 PBAC meeting), the administrative criteria have been updated to allow 11 repeats where the dosing of nivolumab is every two weeks (Q2W), which would provide treatment for 6 months.
	5. The nivolumab dosage in the key CM274 trial was 240 mg 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 proposed maximum amount of nivolumab for this indication was 480 mg, accommodating the longer interval of the Q4W dosing regimen.
	6. The resubmission requested a single restriction for initial and continuing treatment as proposed by the PBAC Secretariat for the previous submission (paragraph 3.7, nivolumab PSD, July 2022 PBAC meeting).
	7. The resubmission proposed several changes or modifications to the restriction wording compared to the previous submission:
* the World Health Organisation (WHO) performance score criterion has been moved from the treatment criteria section to the clinical criteria section to ensure consistency with other nivolumab PBS listings.
* removal of the wording ‘initiated in a patient untreated with programmed cell death-1/ligand-1 (PD-1/PDL-1) inhibitor therapy’ from the clinical criteria as there are no earlier lines of PD-1/PDL-1 therapy currently available in Australian clinical practice. There is a risk of sequential use should immune checkpoint inhibitors subsequently become integrated into the neoadjuvant treatment setting for urothelial carcinoma (UC).
	1. The restriction wording allows for grandfathered patients should the sponsor set up a patient access scheme.
	2. Should nivolumab become available on the PBS for the proposed indication, the existing avelumab restriction in the maintenance setting (following first-line platinum-based chemotherapy) for advanced UC, may need to be amended to require that the patient had not received prior treatment with a PD-(L)1 inhibitor for this condition.

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

1. Population and disease
	1. Bladder cancer is the eleventh most diagnosed cancer in Australia with 25% cases involving muscle invasive disease at diagnosis. MIUC encompasses both muscle invasive bladder cancer (MIBC) and upper tract urothelial cancer (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%)[[4]](#footnote-5). 15% to 25% of UCs either present with or eventually progress to muscle invasive or metastatic disease.
	2. 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 metastatic setting. Similar to MIBC, the prognosis of muscle invasive UTUC is poor with a 5-year disease-specific survival of less than 50%[[5]](#footnote-6).
	3. Current staging of UC uses the tumour-node-metastasis (TNM) system of the American Joint Committee on Cancer (AJCC, 8th edition, 2017).
	4. The resubmission positioned nivolumab as an alternative to watchful waiting in the high risk MIUC adjuvant setting after receipt of prior neoadjuvant chemotherapy and radical surgery.
	5. In the previous submission, feedback was presented from the Genitourinary Advisory Board virtual meeting which indicated that there were relatively few cisplatin-ineligible MIUC patients in clinical practice (BMSA GU Advisory Board Minutes 2021, Attachment 1 accompanying the previous submission).
	6. 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[[6]](#footnote-7). These recommendations are based mainly on results from the randomised POUT[[7]](#footnote-8) 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[[8]](#footnote-9). Except in uncommon circumstances, patients who have received neoadjuvant platinum-based chemotherapy are unlikely to be offered adjuvant platinum-based chemotherapy.
	1. 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.

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

1. Comparator
	1. The resubmission nominated watch and wait surveillance (herein referred to as watchful waiting) as the main comparator. This has not changed from the previous submission. This is appropriate as the target population is now restricted to patients who have previously received NAC. These patients are unlikely to receive adjuvant chemotherapy.

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

1. Consideration of the evidence

Sponsor hearing

* 1. There was no hearing for this item.

Consumer comments

* 1. The PBAC noted and welcomed the input from a health care professional (1) and organisations (2) via the Consumer Comments facility on the PBS website. The health care professional comments described the need for an effective adjuvant therapy for the treatment of urothelial carcinoma after cystectomy and stated the potential for avoiding recurrence with a course of adjuvant nivolumab would provide reassurance to both patients and doctors. Comments from BEAT Bladder Cancer described the impact that living with one of the highest recurring cancers with lowest survival rates has on patients mental health and quality of life. The comments also highlighted improvements in DFS with nivolumab as important for patients and suggested that such treatment was well tolerated with a manageable safety profile.
	2. 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.[[9]](#footnote-10)

Clinical trials

* 1. The resubmission 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.
	2. The ESC noted that the relevant patient population representing the target population in the resubmission is a subgroup of patients in CM274 who had received prior NAC (n = 314).
	3. Details of the key CM274 trial are provided in Table 4.

Table 4: **Trials and associated reports presented in the resubmission.**

| **Trial ID** | **Protocol title/ Publication title** | **Publication citation** |
| --- | --- | --- |
| CA209274(CheckMate 274 (CM274)) (NCT02632409) | Extended follow-up for Study CA209274. A Phase 3 Randomised, Double-blind, Multi-centre Study of Adjuvant NIVO versus Placebo in Subjects with High-Risk Invasive Urothelial Carcinoma. Extended follow-up(CM274 Database Lock October 2022; data cut-off September 2022) | 22 October 2022 |
| 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 AdjuvantNivolumab versus Placebo in Subjects with High risk Invasive UrothelialCarcinoma | 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) 22nd Annual Meeting, December 1–3, 2021. |

Source: Table 2.4, p28 of the submission

Blue shading indicates publications previously seen by the PBAC.

* 1. The key features of the CM274 trial are summarised in Table 5.

**Table 5: 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 | Ra, DBData cutoff in previous submission February-2021 Median follow-upNIVO: 24.4 monthsPBO: 22.51 monthsData cutoff in resubmission September 2022Median follow-up: 36.1 monthsNIVO: 37.4 monthscPBO: 33.9 monthsc | Low | Adjuvant settingUndergone radical surgical resection for MIUC.Prior NAC: Stage ypT2-ypT4a or ypN+No prior NAC and were ineligible/declined adjuvant cisplatin chemotherapy: pT3-pT4a or pN+ | Primary: DFSSecondary: NUTRFS, OSb, and DSSbExploratory: DMFSPrimary analysis populations:ITT and the PD-L1 ≥ 1% subgroupTarget PBS population in resubmission:Prior NAC subgroup | Only trial-based DFS data used |

Source: para 6.6, nivolumab PSD, July 2022 PBAC meeting and Sections 1 and 2 of the resubmission.

DB = double blind; DFS = disease free survival; DMFS = distant metastasis-free survival; DSS = disease specific survival; NAC = neoadjuvant cisplatin chemotherapy; NIVO = nivolumab; NUTRFS = non upper tract recurrence free survival; OS = overall survival; PBO = placebo; PD-L1 = programmed cell death ligand 1; 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% *vs.* < 1% *vs.* indeterminate); and prior use of cisplatin neoadjuvant chemotherapy (yes *vs.* no).

bOS and DSS data for extended follow-up (September 2022 data cut-off) were not provided in the resubmission.

cSourced from Galsky MD et al. Extended follow-up results from the CheckMate 274 trial. ASCO Genitourinary Cancers Symposium 2023. Abstract LBA443

Blue shading indicates publications previously seen by the PBAC

* 1. 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”.
	2. 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.
	1. 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) Eastern Cooperative Oncology Group (ECOG) performance status score of 2, and iv) New York Heart Association Class III or IV heart failure.
	2. 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.
	3. 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% *vs.* < 1% *vs.* indeterminate); and prior use of NAC (yes *vs.* no). Less than 2% of patients enrolled in the CM274 trial were classified as PD-L1 indeterminate or not evaluable.
	4. 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). The resubmission did not provide updated OS data for the September 2022 data cutoff and argued that the data remain immature. The PSCR stated that ‘as mature OS data is event driven, it is not currently available nor expected for several years’ and in the absence of OS data the resubmission sought to address the clinical and cost-effectiveness uncertainties caused by a lack of long-term OS data. The ESC considered the provision of all available short-term OS data would assist with reducing the uncertainties caused by the lack of long-term OS data. The pre-PBAC response stated that it was unable to provide mature OS data and re-iterated its PSCR argument regarding the approach taken by the resubmission in the absence of this data.
	5. The requested target PBS population in the resubmission is restricted to patients who have received prior NAC. Thus, outcomes were presented only for the prior NAC subgroup (and the complement of no prior NAC subgroup for comparative purposes) of CM274. Although the relevant population is the prior NAC subgroup of the CM274 trial, the risk of bias was considered low, as prior NAC use was a stratification factor at randomisation in the trial. Baseline demographic and disease characteristics for the prior NAC subgroup were reasonably balanced between the nivolumab and placebo arms.
	6. There were limited data provided in the resubmission on subsequent anti-cancer treatments in CM274. Table 6 presents a summary of subsequent anti-cancer treatments reported for the nivolumab and placebo arms in the prior NAC subgroup of CM274 trial. The proportion of patients by type of subsequent therapy received was estimated based on the number of patients randomised, not patients who experienced recurrence.

Table 6: CM274 - Subsequent anti-cancer therapies in the neoadjuvant platinum-based chemotherapy subgroup (data cutoff: 08 September 2022)

| **Type of subsequent therapy** | **All randomised patients with prior neoadjuvant platinum-based chemotherapy** |
| --- | --- |
| **Nivolumab (N=156)**  | **Placebo (N=158)** |
| Anya | 57 (36.5%) | 78 (49.4%) |
| Radiotherapy | 16 (10.3%) | 18 (11.4%) |
| Surgery | 7 (4.5%) | 9 (5.7%) |
| Systemic therapy | 47 (30.1%) | 73 (46.2%) |
| Immunotherapy | 10 (6.4%) | 61 (38.6%) |
| Platinum-based chemotherapy | 29 (18.6) | 18 (11.4%) |
| Patients with > 1 dose of subsequent intravesical chemotherapy  | 0 (0.0%) | 2 (1.3%) |
| Patients with 1 dose of subsequent intravesical chemotherapy | 2 (1.3%) | 1 (0.6%) |

Source: Table 17, p52 of the resubmission.

a Patients may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomisation date if patient never treated).

Note: Proportions based on number of patients randomised to each arm rather than on number of patients with recurrence only; data based on extended follow-up (data cutoff 08 September 2022). Minimum duration of follow-up: 31.6 months)

* 1. Among randomised patients in the prior NAC subgroup (updated data cutoff September 2022), subsequent anti-cancer therapy was received by 36.5% of patients in the nivolumab arm and 49.4% in the placebo arm. The most common form of subsequent anti-cancer therapy was systemic therapy (30.1% and 46.2% in the nivolumab and placebo arms, respectively). A higher proportion of patients in the placebo arm received immunotherapy compared to the nivolumab arm (38.6% *vs*. 6.4%). The most frequent subsequent immunotherapies received were pembrolizumab, atezolizumab, and nivolumab.
	2. Among patients who experienced recurrence in the prior NAC subgroup (estimated as the number of patients with a DFS event minus the number of pre-recurrence deaths), the proportion of patients who subsequently received immunotherapy post recurrence was 13.3% (10/75) in the nivolumab arm and 59.8% (61/102) in the placebo arm. Similarly, the proportion of patients who received platinum-based chemotherapy post recurrence was 38.7% (29/75) in the nivolumab arm and 17.6% (18/102) in the placebo arm.
	3. Sequential use of immunotherapy as observed for the nivolumab arm is not indicated in Australian clinical practice. Immunotherapy is typically restricted to one regimen for a patient’s entire treatment course. Furthermore, noting the modest proportion of patients in the placebo arm who received subsequent platinum-based chemotherapy, it is also uncertain whether subsequent use of immunotherapy in the placebo arm is reflective of expected use in the Australian setting 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 or in the second-line setting with pembrolizumab after failure on platinum-based chemotherapy[[10]](#footnote-11). The overall impact of subsequent anti-cancer treatments in CM274 on OS results remain unclear from the available data.

Comparative effectiveness

* 1. The resubmission noted that as the OS data remain immature, an updated analysis of OS was not presented. However, the ESC agreed with the evaluation that OS results based on the most recent data cutoff (September 2022) would have been informative. The ESC noted that in the prior NAC subgroup, at the time of the September 2022 data cutoff, 64 deaths (41.0%) and 81 deaths (51.3%) had occurred in the nivolumab and placebo arms, respectively (updated CM274 data report, Attachment 8 accompanying the resubmission).
	2. In the July 2022 PBAC consideration of nivolumab for this indication, the ESC noted 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, particularly 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 (paragraph 6.40, nivolumab PSD, July 2022 PBAC meeting).
	3. The PBAC previously also 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, in July 2022 the PBAC considered that longer-term data are required to determine whether the observed improvement in DFS translates into a clinically meaningful OS benefit (paragraph 7.5, nivolumab PSD, July 2022 PBAC meeting). The ESC noted the PSCR stated that ‘as mature OS data is event driven, it is not currently available nor expected for several years’ and that DFS is considered a patient-relevant and clinically meaningful endpoint in the adjuvant setting. The ESC considered that the primary goal of adjuvant therapy is to improve cure rates and long-term OS data are required to confirm improved cure rates and a relationship between DFS and OS.
	4. Results for the primary endpoint of DFS in the prior NAC subgroup are summarised in Table 7. The DFS results are for the September 2022 data cutoff, with a median duration of follow-up 36.1 months for the CM274 ITT population (37.4 months in the nivolumab arm and 33.9 months in the placebo arm)[[11]](#footnote-12). DFS results for the complement (no prior NAC) has been included for comparative purposes. Use of prior NAC was a stratification factor at randomisation (yes *vs*. no) in the CM274 trial.
	5. The ESC noted that DFS data for the September 2022 data cutoff were provided in the resubmission and considered the updated data was consistent with the previous data-cutoff, noting that the confidence interval for the no prior NAC group continues to contain the null value.

Table 7: Primary efficacy results: DFS – by use of prior NAC

|  |  |  |
| --- | --- | --- |
| **DFS parameters**  | **Prior NAC**  | **No prior NAC** |
| **NIVO (N=156)** | **PBO (N=158)** | **NIVO (N=197)** | **PBO (N=198)** |
| Events, n (%) | 82 (52.6) | 113 (71.5) | 113 (57.3) | 120 (60.6) |
| Median DFS (95% CI), monthsa | 25.8 (16.3, 55.2) | 8.2 (5.6, 10.8) | 21.2 (17.7, 28.3) | 16.7 (8.5, 25.6) |
| HRb (95% CI); p-valuec | 0.54 (0.41, 0.72); p<0.0001 | 0.88 (0.68, 1.14); p=0.3336 |
| Rate at 3 monthsa, % (95% CI) | 87.5 (81.1, 91.8) | 68.0 (60.0, 74.7) | 86.4 (80.7, 90.5) | 76.4 (69.7, 81.8) |
| Rate at 6 monthsa, % (95% CI) | 78.2 (70.7, 84.0) | 53.9 (45.7, 61.3) | 72.7 (65.8, 78.5) | 64.8 (57.6, 71.2) |
| Rate at 12 monthsa,d, % (95% CI) | 67.4 (59.2, 74.3) | 39.5 (31.8, 47.1) | 60.4 (53.0, 66.9) | 53.5 (46.1, 60.3) |
| Rate at 24 monthsa,d, % (95% CI) | 50.8 (42.5, 58.5) | 33.5 (26.1, 41.0)  | 46.4 (39.0, 53.5) | 43.3 (36.0, 50.3) |
| Rate at 30 monthsa,d, % (95% CI) | 49.4 (41.1, 57.2) | 30.6 (23.4, 38.0) | 42.1 (34.8, 49.2) | 40.4 (33.2, 47.4)  |

Source: Table 23, p64 of the resubmission and Galsky et al (2023).

CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; NAC = neoadjuvant platinum-based chemotherapy; NIVO = nivolumab; PBO = placebo.

Notes: 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.

Data based on the extended follow-up (data cutoff on 08 September 2022). Median follow-up 36.1 months for the ITT population (NIVO: 37.4 months; PBO: 33.9 months). Median follow-up duration by arm sourced from Galsky MD et al. Extended follow-up results from the CheckMate 274 trial. ASCO Genitourinary Cancers Symposium 2023. Abstract LBA443)

a Based on Kaplan-Meier estimates.

b Unstratified Cox proportional hazards model. HR is NIVO over PBO.

c Unstratified log-rank test.

d Provided in Table 1 of PSCR

* 1. For patients who had received prior NAC, the median duration of DFS was 25.8 months in the nivolumab arm (95% confidence interval (CI): 16.3, 55.2) and 8.2 months in the placebo arm (95% CI: 5.6, 10.8). This difference (17.6 months) corresponded to a statistically significant 46% reduction in the hazard of recurrence or death favouring nivolumab (hazard ratio (HR): 0.54, 95% CI: 0.41, 0.72). At 6 months, the DFS rates (Kaplan Meier (KM) event-free rates) were 78.2% and 53.9% (difference of 24.3%) in the nivolumab and placebo arms, respectively. The PSCR provided DFS rates up to 30 months (Table 7).
	2. The observed magnitude of DFS benefit associated with nivolumab over placebo was much smaller in the complement ‘no prior NAC’ subgroup. The reduction in hazard of recurrence or death associated with nivolumab versus placebo was a modest 12% which was not statistically significant (difference in median DFS: 4.5 months; HR: 0.88, 95% CI: 0.68, 1.14). Notably, the median DFS duration in the placebo arm of the ‘no prior NAC’ subgroup (16.7 months) was at least two-fold longer that observed in the placebo arm of the prior NAC subgroup (8.2 months). On the other hand, the median DFS in the nivolumab arm was longer in the prior NAC (25.8 months) versus no prior NAC (21.2 months) subgroups. There were remarkable differences in baseline characteristics between the prior NAC and no prior NAC patient populations which make comparisons difficult. For example, for the placebo arms in the prior NAC vs. no prior NAC subgroups, differences included (non-exhaustive) patient’s age < 65 years (53.2% vs. 26.3%), Asian race (12.7% vs. 27.8%), ECOG PS of 0 (69.6% vs. 56.1%), UTUC tumour type (8.2% vs. 31.3%), pathological stage pT3/pT4a at resection (58.9% vs 87.4%), and nodal stage at resection (N0/X with <10 nodes removed: 16.5% vs. 36.9%; N3: 9.5% vs. 2.5%).
	3. For comparative purposes, the KM curves for DFS in the ITT population presented in the previous submission (data cutoff February 2021) and the KM curves for the prior NAC subgroup presented in the resubmission (data cutoff September 2022) are depicted in Figure 1. No KM curves for DFS were provided in the resubmission for the no prior NAC subgroup.

Figure 1: CM274 – Kaplan-Meier curves for DFS – ITT population (previous submission) vs. prior NAC subgroup (resubmission)



Source: Compiled during the evaluation from Figure 5, p65 of the resubmission and Figure 12, p72 of the previous submission (considered at the July 2022 PBAC meeting).

DFS = disease-free survival; ITT = intention-to-treat; NAC = neoadjuvant platinum-based chemotherapy; Nivo = nivolumab; PBO = placebo

aPrevious submission: Data cutoff was February 2021 (median follow-up Nivo 24.4 months and PBO 22.5 months)

bResubmission: Data cutoff was September 2022. Median follow-up for the ITT 36.1 months (Nivo 37.4 months and PBO 33.9 months)

* 1. Results for the secondary/exploratory outcomes of NUTRFS and DMFS by prior use of NAC, at the updated data cutoff September 2022, are summarised in Table 8. The corresponding KM curves for NUTRFS and DMFS are presented in Figure 2 and Figure 3, respectively.

Table 8: CM274 - Secondary/exploratory outcomes of NUTRFS and DMFS – by use of prior NAC

|  |  |  |
| --- | --- | --- |
| **Efficacy parameters**  | **Prior NAC**  | **No prior NAC** |
| **NIVO (N=156)** | **PBO (N=158)** | **NIVO (N=197)** | **PBO (N=198)** |
| **NUTRFS** |
| Events, n (%) | 80 (51.3) | 107 (67.7) | 104 (52.8) | 110 (55.6) |
| Median NUTRFS (95% CI), monthsa | 33.4 (16.5, NE) | 8.3 (5.8, 11.9) | 25.9 (19.4, 41.8) | 21.2 (13.7, 39.9) |
| HRb (95% CI) | 0.57 (0.43, 0.76) | 0.89 (0.68, 1.16) |
| Rate at 3 monthsa, % (95% CI) | 87.5 (81.1, 91.8) | 70.3 (62.5, 76.9) | 88.0 (82.4, 91.8) | 80.6 (74.3, 85.6) |
| Rate at 6 monthsa, % (95% CI) | 78.8 (71.4, 84.5) | 56.6 (48.4, 64.0) | 75.8 (69.1, 81.3) | 67.4 (60.2, 73.5) |
| **DMFS** |
| Events, n (%) | 69 (44.2) | 85 (53.8) | 86 (43.7) | 92 (46.5) |
| Median DMFS (95% CI), monthsa | 48.2 (21.9, N.A.) | 15.2 (8.3, 47.8) | 41.1 (23.8, NE) | 39.9 (20.0, NE) |
| HRb (95% CI) | 0.62 (0.45, 0.85) | 0.88 (0.65, 1.18) |
| Rate at 3 monthsa, % (95% CI) | 90.7 (84.8, 94.4) | 75.5 (67.9, 81.5) | 91.1 (86.0, 94.4) | 83.7 (77.6, 88.2) |
| Rate at 6 monthsa, % (95% CI) | 83.0 (75.9, 88.2) | 63.7 (55.4, 70.8) | 82.4 (76.1, 87.1) | 74.1 (67.2, 79.8) |
| Rate at 12 monthsa, % (95% CI) | 74.4 (66.4, 80.7) | 52.1 (43.6, 60.0)  | 69.7 (62.4, 75.9) | 63.9 (56.4, 70.5) |
| Rate at 24 monthsa, % (95% CI) | 58.4 (49.7, 66.1) | 46.9 (38.3, 55.0)  | 57.4 (49.5, 64.4) | 54.7 (46.9, 61.9) |
| Rate at 30 monthsa, % (95% CI) | 56.1 (47.3, 63.9) | 44.0 (35.3, 52.2) | 53.8 (45.8, 61.0) | 51.9 (44.0, 59.2) |

Source: Table 24, p66 of the resubmission

CI = confidence interval; DMFS = distant metastasis-free survival; HR = hazard ratio; NAC = neoadjuvant platinum-based chemotherapy; NIVO = nivolumab; NE = not estimable (not reached); NUTRFS = non-urothelial tract recurrence-free survival; PBO = placebo.

Data cut-off September 2022. Median follow-up for the ITT population 36.1 months.

a Based on Kaplan-Meier estimates.

b Unstratified Cox proportional hazard model. HR for NIVO versus PBO.

c Provided in Table 2 of PSCR

Figure 2: CM274 - Kaplan-Meier plot of NUTRFS – Prior neoadjuvant platinum-based chemotherapy population



Source: Figure 6, p67 of the resubmission.

CI = confidence interval; HR = hazard ratio; NA = not estimable (not reached); NUTRFS = non-urothelial tract recurrence-free survival.

Notes: Statistical model for hazard ratio and p-value - stratified Cox proportional hazard and stratified log-rank test.

Symbols represent censored observations.

Unstratified Cox proportional hazards model. HR is NIVO over PBO.

Data based on the extended follow-up (Data cutoff on 08 September 2022, Median follow-up, 36.1 months)

Figure 3: CM274 - Kaplan-Meier plot of DMFS – Prior neoadjuvant platinum-based chemotherapy population

Source: Figure 7, p68 of the resubmission.

CI = confidence interval; DMFS = distant metastases-free survival; HR = hazard ratio; NA = not estimable (not reached)

Notes: Statistical model for hazard ratio and p-value - stratified Cox proportional hazard and stratified log-rank test.

Symbols represent censored observations.

Unstratified Cox proportional hazards model. HR is NIVO over PBO.

Data based on the extended follow-up (Data cut-off on 08 September 2022, Median follow-up, 36.1 months)

* 1. In the prior NAC subgroup, nivolumab was associated with a statistically significant 43% reduction in the hazard of non-urothelial tract recurrence or death compared with placebo (HR: 0.57, 95% CI: 0.43, 0.76). The median duration of NUTRFS was 33.4 months in the nivolumab arm and 8.3 months in the placebo arm (difference of 25.1 months). The NUTRFS event-free rate at 6 months was higher in the nivolumab arm (78.8%) than in the placebo arm (56.6%).
	2. The observed magnitude of NUTRFS benefit associated with nivolumab over placebo was much smaller in the complement population with no prior NAC. The reduction in hazard of non-urothelial tract recurrence or death compared with placebo was 11% which was not statistically significant (difference in median DFS: 4.7 months; HR 0.89, 95% CI: 0.68, 1.16). Notably, as was the case for DFS, the median NUTRFS duration in the placebo arm was substantially longer in the no prior NAC (21.2 months) than in the prior NAC (8.3 months) subsets. On the other hand, the median NUTRFS duration in the nivolumab arm was longer in the prior NAC (33.4 months) versus no prior NAC (25.9 months) subsets.
	3. In the prior NAC subgroup, nivolumab was associated with a statistically significant 38% reduction in the hazard of distant metastases or death compared with placebo (HR: 0.62, 95% CI: 0.45, 0.85). The median duration of DMFS was longer in the nivolumab arm than in the placebo arm (48.2 months *vs.* 15.2 months; difference 33 months).
	4. As was the case for both DFS and NUTRFS, the observed magnitude of DMFS benefit associated with nivolumab over placebo was much smaller in the complement no prior NAC subgroup. The reduction in hazard of distant metastases or death versus placebo was 12% which was not statistically significant (median DFS: 41.1 months vs. 39.9 months (difference 1.2 months); HR: 0.88, 95% CI: 0.65, 1.18). The median DMFS duration in the placebo arm was substantially longer in the no prior NAC (39.9 months) than in the prior NAC (15.2 months) subgroups. On the other hand, the median DMFS duration in the nivolumab arm was longer in the prior NAC (48.2 months) versus no prior NAC (41.1 months) subgroups.
	5. Health-related quality of life (HRQoL) data from the CM274 trial were based on the September 2022 data cutoff. The resubmission noted that HRQoL outcomes were only available for all treated patients in the prior NAC subgroup. The resubmission did not report on the percentage of patients that completed the EORTC QLQ[[12]](#footnote-13)-C30 in both treatment arms. The resubmission noted that at baseline, mean EORTC QLQ-C30 summary scores for all domains were comparable between treatment arms.
	6. Overall, HRQoL results were similar to those presented for the ITT population in the previous submission. Changes from baseline in the EORTC QLQ-C30 global health status and the EQ-5D-3L visual analogue scale scores over time indicated that there was no meaningful difference in deterioration in quality of life (QoL) between patients who received nivolumab and those who received placebo. No statistical tests were performed on change from baseline scores between treatment arms.
	7. In the previous consideration of nivolumab for MIUC, it was noted that although EORTC QLQ-C30 and EQ-5D scales have become international standards for HRQoL measurement, 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 usually 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. In July 2022, the PBAC considered that the HRQoL results did not reflect the higher rate of toxicity in the nivolumab treatment arm compared to placebo in the CM274 trial (paragraph 6.32, nivolumab PSD, July 2022 PBAC meeting). This is a similar concern in the resubmission for the prior NAC patient population.
	8. The PBAC previously noted that atezolizumab (a PD-L1 inhibitor) has been assessed in a randomised controlled trial as an adjuvant treatment in a similar patient population with MIUC at a high risk of recurrence after radical cystectomy or nephroureterectomy (IMvigor010)[[13]](#footnote-14). In this trial, 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 was 19.4 months with atezolizumab and 16.6 months with observation (HR: 0.89; 95% CI: 0.74, 1.08). The PBAC previously noted that the results for this trial 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 (paragraph 4.9, nivolumab PSD, July 2022 PBAC meeting).
	9. In the prior NAC patient subgroup (n=385) of IMvigor010, the median DFS duration was 19.8 months with atezolizumab and 16.5 months with observation (HR: 0.87, 95% CI: 0.66, 1.15). In the no prior NAC subgroup (n=424), the median DFS duration was 16.8 months with atezolizumab and 19.4 months with observation (HR: 0.98, 95% CI: 0.75, 1.28).
	10. Results from an ongoing Phase III randomised controlled trial comparing pembrolizumab (PD-1 inhibitor) as an adjuvant treatment with observation in patients with MIUC at a high risk of recurrence (AMBASSADOR; NCT03244384) are expected in June 2025.

Comparative harms

* 1. Table 9 summarises the results of safety outcomes for the prior NAC subgroup in the CM274 trial during the on-treatment period (September 2022 data cutoff, median duration of follow-up 36.1 months; mean duration of nivolumab treatment 8.2 months [based on the Q2W dosing regimen in the CM274 trial]).

Table 9: CM274 – Overview of clinical AEs across treatment groups – All treated patients with prior neoadjuvant platinum-based chemotherapy

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category**  | **NIVO (N=155)** **n (%)** | **PBO (N=156),n (%)** | **Risk ratio****[95% CI]** | **Risk difference, proportion,****[95% CI]** |
| **All causality** |
| AE (any grade) | 153 (98.7%) | 149 (95.5%) | 1.0 [1.0, 1.1] | 0.03 [-0.01, 0.07] |
| Severe AE (grade 3 or 4) | 64 (41.3%) | 58 (37.2%) | 1.1 [0.8, 1.5] | 0.04 [-0.07, 0.15] |
| SAE (any grade) | 47 (30.3%) | 50 (32.1%) | 1.0 [0.7, 1.3] | -0.02 [-0.12, 0.09] |
| Severe SAE (grade 3 or 4) | 39 (25.2%) | 32 (20.5%) | 1.2 [0.8, 1.9] | 0.05 [-0.05, 0.14] |
| Discontinuation of study treatment due to AEs (any grade) Severe AEs (grade 3 or 4) | 28 (18.1%)15 (9.7%) | 17 (10.9%)10 (6.4%) | 1.6 [1.0, 2.9]1.5 [0.7, 3.3] | 0.07 [-0.01, 0.15]0.03 [-0.03, 0.09] |
| Death | 95 (27.1%) | 107 (30.7%) | 0.9 [0.7, 1.1] | -0.04 [-0.10, 0.03] |
| **Study drug related** |
| AE (any grade) | 127 (81.9%) | 82 (52.6%) | **1.6 [1.3, 1.8]** | **0.30 [0.20, 0.40]** |
| Severe AE (grade 3 or 4) | 23 (14.8%) | 6 (3.8%) | **3.9 [1.6, 9.2]** | **0.11 [0.05, 0.17]** |
| SAE (any grade) | 11 (7.1%) | 3 (1.9%) | **3.7 [1.1, 13.0]** | **0.05 [0.01, 0.10]** |
| Severe SAE (grade 3 or 4) | 10 (6.5%) | 2 (1.3%) | **5.0 [1.1, 22.6]** | **0.05 [0.01, 0.09]** |
| Discontinuation of study treatment due to AEs (any grade) Severe AEs (grade 3 or 4) | 18 (11.6%)8 (5.2%) | 1 (0.6%)0 | **18.1 [2.5, 134.0]****17.1 [1.0, 293.9]** | **0.11 [0.06, 0.16]****0.05 [0.01, 0.09]** |

Source: Table 25, p72 of the resubmission

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

Notes: Results in **bold** indicate statistically 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.

Data based on September 2022 data cutoff

* 1. 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. Furthermore, the CM274 trial was not powered to detect statistically significant differences in adverse events (AEs) between the nivolumab and placebo arms. Thus, non-statistically significant differences are not necessarily reflective of clinically irrelevant findings.
	2. AEs were reported in almost all prior NAC patients in both treatment arms (98.7% in the nivolumab arm, 95.5% in the placebo arm). The risk ratios (RRs) and risk differences (RDs) were statistically significant favouring placebo over nivolumab for the following study drug-related AEs:
* AEs of any grade (RR: 1.6 [95% CI: 1.3, 1.8]).
* Serious AEs (SAEs), any grade (RR: 3.7 [95% CI: 1.1, 13.0]).
* Severe Grade 3-4 AEs (RR: 3.9 [95% CI: 1.6, 9.2]).
* Severe Grade 3-4 SAEs (RR: 5.0 [95% CI: 1.1, 22.6]); and
* Treatment discontinuation due to a Grade 3-4 severe AE (RR: 17.1 [95% CI: 1.0, 293.9]).
	1. The most common drug-related AEs reported in the nivolumab versus placebo arms were pruritus (21.9% *vs.* 9.6%), fatigue (21.9% *vs.* 13.5%), diarrhoea (19.4% *vs.* 16.0%), rash (14.8% *vs.* 6.4%), and hypothyroidism (12.9% *vs.* 1.9%). Study drug-related severe AEs included increased lipase level (4.5% *vs.* 0.6%) and increased amylase level (3.2% vs. 0.6%).
	2. Adverse events of special interest (AESIs) were not discussed in the resubmission. In the CM274 protocol, these were specified as demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, myocarditis, myositis, pancreatitis, rhabdomyolysis, graft versus host disease and uveitis.
	3. From the data presented in the resubmission, overall, no new safety issues were identified, and the safety profile appears consistent with the previously documented safety profile of nivolumab monotherapy.

Benefits/harms

* 1. A summary of the comparative benefits and harms for nivolumab versus placebo in the prior NAC subgroup is presented in Table 10.

Table 10: Summary of the comparative benefits and harms for nivolumab versus placebo (proxy for watchful waiting) in the prior neoadjuvant platinum-based chemotherapy population

| Benefits  |
| --- |
|  | NivolumabN=156 | PlaceboN=158 | Absolute difference | HR (95% CI)p-value |
| DFS (primary outcome) |
| Recurrence or death, n (%) | 82 (52.6) | 113 (71.5) |  | 0.54(0.41, 0.72)p<0.0001a |
| Median DFS, months (95% CI) | 25.8 (16.3, 55.2) | 8.2 (5.6, 10.8) | 17.6 months |
| DFS rate at 6 months, % (95% CI)b | 78.2 (39.0, 50.7) | 53.9 (45.7, 61.3) | 24.3% |
| DFS rate at 12 months, % (95% CI)b,c | 67.4 (59.2, 74.3) | 39.5 (31.8, 47.1) | 27.9% d |
| DFS rate at 24 months, % (95% CI b,c | 50.8 (42.5, 58.5) | 33.5 (26.1, 41.0)  | 17.3% d |
| DFS rate at 30 months, % (95% CI)b,c | 49.4 (41.1, 57.2) | 30.6 (23.4, 38.0) | 18.8% d |
| DMFS (exploratory outcome) |
| Distant recurrence or death, n (%)  | 69 (44.2) | 85 (53.8) |  | 0.62(0.45, 0.85) |
| Median DMFS, months (95% CI) | 48.2 (21.9, NE) | 15.2 (8.3, 47.8) | 33.0 months |
| DMFS rate at 6 months,% (95% CI)b  | 83.0 (75.9, 88.2) | 63.7 (55.4, 70.8) | 19.3% |
| DMFS rate at 12 months, % (95% CI)b,c | 74.4 (66.4, 80.7) | 52.1 (43.6, 60.0)  | 22.3% d |
| DMFS rate at 24 months, % (95% CI b,c | 58.4 (49.7, 66.1) | 46.9 (38.3, 55.0)  | 11.5% d |
| DMFS rate at 30 months, % (95% CI)b,c | 56.1 (47.3, 63.9) | 44.0 (35.3, 52.2) | 12.1% d |
| **Harms** **– Safety evaluable population (mean duration of treatment: nivolumab 8.2 months (based on Q2W dosing regimen))** |
| **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 AE | 23/155 | 6/156 | 3.9(1.6, 9.2) | 14.8% | 3.8% | 11%(5%, 17%) |
| Grade 3-4 study drug-related severe SAE | 10/155 | 2/156 | 5.0(1.1, 22.6) | 6.5% | 1.3% | 5%(1%, 9%) |
| Any grade study drug-related pruritus | 34/155 | 15/156 | 2.3(1.3, 4.0) | 21.9% | 9.6% | 12%(4%, 20%) |

Source: Tables 24−26, pp64-76 of the resubmission

AE = adverse event; CI = confidence interval; DFS = disease-free survival; DMFS = distant metastasis-free survival; HR = hazard ratio; NE = not estimable (not reached); Q2W/Q4W = every 2/4 weeks; RD = risk difference; RR = relative risk; SAE = serious adverse event.

Notes:

September 2022 data cutoff, median duration of follow-up: 36.1 months (nivolumab: 37.4 months; placebo: 33.9 months).

No analysis of overall survival data was provided in resubmission.

HRs for DFS and DMFS were for nivolumab versus placebo. HRs <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 (treated with at least one dose of study drug).

a Unstratified log-rank test. p-value provided only for primary outcome of DFS.

b Based on Kalan-Meier estimates.

c Provided in Table 1 and Table 2 of PSCR

d Calculated based on values provided in the PSCR

* 1. On the basis of the direct evidence presented in the resubmission, for every 100 patients treated with nivolumab in comparison with placebo (median duration of follow-up: 36.1 months [nivolumab: 37.4 months; placebo: 33.9 months]):
* Approximately 24 additional patients will remain free of disease recurrence or death at 6 months.
* Approximately 5 additional patients will experience a life-threatening or severe serious adverse event.
* Approximately 12 additional patients will experience pruritus (any grade).

The ESC noted that the impact on OS is unknown.

Clinical claim

* 1. Based on the direct comparison in the CM274 trial, the resubmission described adjuvant treatment with nivolumab in patients who have received prior NAC and have undergone radical resection of MIUC, and are at high risk of recurrence, as superior in terms of effectiveness and inferior in terms of safety compared to placebo (as a proxy for watchful waiting).
	2. The resubmission noted that OS data from CM274 remain immature and argued that:
* reducing the risk of cancer recurrence is a meaningful clinical benefit, particularly among patients at high risk of disease recurrence and that the DFS endpoint is not confounded by subsequent anti-cancer therapies as is the case for OS;
* for exploratory endpoints such as NUTRFS and DMFS, nivolumab was associated with clinically meaningful risk reductions compared with placebo; and
* the results for patient-reported endpoints, including EORTC QLQ-C30 and EQ-5D-3L, demonstrated that adjuvant treatment with nivolumab was not detrimental to patients’ HRQoL compared to placebo.
	1. For efficacy, the ESC considered that the therapeutic conclusion presented in the resubmission is likely reasonable in terms of DFS from the CM274 trial evidence. However, the ESC considered that as no analysis of OS data was provided in the resubmission, a claim of superiority in terms of OS benefit cannot be made. Longer-term OS data are required to conclusively determine whether the observed improvement in DFS translates into a clinically meaningful OS benefit.
	2. The ESC considered that the claim of inferior safety compared to placebo was reasonable and adequately supported by the AE data.
	3. The EORTC QLQ-C30 and EQ-5D-3L data indicated there was no meaningful difference in deterioration in QoL between patients in the nivolumab and placebo arms of the CM274 trial. However, the evaluation considered these tools were limited in capturing the impact of immunotherapy on a patient’s HRQoL.
	4. The PBAC considered that the claim of superior comparative effectiveness in terms of DFS was reasonable.
	5. The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

* 1. The resubmission presented an updated modelled economic evaluation, based on the CM274 trial, which compared treatment with nivolumab versus watchful waiting in the high risk MIUC adjuvant setting after receipt of prior NAC and radical surgery. The types of economic evaluation presented were a cost-effectiveness analysis and a cost-utility analysis, measuring outcomes in terms of life years (LYs) gained and quality-adjusted life years (QALYs) gained, respectively. This is unchanged since the previous submission.
	2. The key components of the economic evaluation and changes compared with the previous submission are summarised in Table 11.

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

| Component | Summary |
| --- | --- |
| Population | Patients with MIUC who have undergone radical resection surgery and are at high risk of recurrence, and who have received prior NAC. This was changed since the previous submission which did not restrict to those patients who had received prior NAC. This change was consistent with advice provided by the PBAC previously (para 7.11, nivolumab PSD, July 2022 PBAC meeting). |
| Treatments | Adjuvant nivolumab treatment *vs* watchful waiting |
| Time horizon | 20 years in the model base case versus median 36.1 month follow-up at the updated September 2022 data cut-off (ITT population) of the CM274 trial. The time horizon was unchanged from the previous submission and may not be reasonable as the PBAC requested more conservative assumptions regarding the time horizon be applied (para 7.9, nivolumab PSD, July 2022 PBAC meeting). |
| Outcomes | LYs and QALYs gained |
| Methods used to generate results | Cohort expected value analysis (Markov model). This was previously justified on the basis of immature OS data from CM274. At the more recent data cutoff of September 2022, 64 deaths (41.0%) and 81 deaths (51.3%) had occurred in the nivolumab and placebo arms, respectively, in the prior NAC subgroup. The use of trial-based OS data directly in the model could reduce the reliance of the model on these assumptions. |
| Health states | Four health states: pre-recurrence, locoregional recurrence, distant recurrence and dead. This was changed from the previous submission which included only three health states due to concerns noted by the PBAC on the granularity of the model structure (para 7.11, nivolumab PSD, July 2022 PBAC meeting). The revisions in model structure were not a main driver of changes in the incremental costs or outcomes modelled. |
| Cycle length | First year: 4 weeksSubsequent years: 3-monthly |
| Transition probabilities | The probability of remaining in pre-recurrence was based on DFS data from the prior NAC subgroup of CM274. The evaluation considered that this was reasonable. Patients were assumed to be cured after five years. Data from CM274 were also used to inform the type of first recurrence event (locoregional or distant) and transitions from the locoregional health state to dead or distant recurrence (both assumed to be fixed over time and did not vary across model arms).Background mortality in pre-recurrence was based on Australian life tables (2019-21), with an increased risk of death applied for the first five years (1.8x) (increased from 1.5x over first two years). No justification was provided for limiting the duration of increased risk and this may not be reasonable. Expert opinion was used to determine the proportion of recurrence events that resulted in a cure (which varied by type of recurrence and model arm) (locoregional recurrence: 6.6% and 7.7%, nivolumab and watchful waiting, respectively; and distant recurrence: 2.7% and 4.2%, respectively). Survival estimates from external trials[[14]](#footnote-15),[[15]](#footnote-16),[[16]](#footnote-17) were used to inform the transition from distant recurrence to dead. Differences were noted in the patient characteristics between these trials. Inferring differences in survival outcomes across these studies is highly uncertain. |
| Extrapolation method | DFS data from the prior NAC subgroup of CM274 were extrapolated from 54 months using Gompertz models independently fitted to the data (previously 29.5 months using independent generalised gamma models). The truncation point chosen to extrapolate DFS in the comparator arm may be too late, as the observed data at this time point are unreliable. The generalised gamma model provided a better fit, both statistically and by visual inspection, to the nivolumab data. The ESC noted that 79% of the incremental QALYs gained were accrued in the extrapolated period. |
| Health related quality of life | EQ-5D-3L data collected in the CM274 trial (prior NAC subgroup) using Australian preferences[[17]](#footnote-18). Least square mean change scores from baseline (0.824) were applied to estimate health state utility values (disease-free: -0.004; local recurrence: -0.124; distant recurrence: -0.093). These resulted in a lower utility applied for locoregional than distant recurrence. The ESC considered that this was not reasonable. The changes from baseline between the recurrence states had overlapping confidence intervals, and so a difference in utility based on these data may not be reasonable. A one-off disutility for AEs was also applied on model entry (nivolumab: −0.00253; WW: −0.0003). Some of the disutility values used may be an underestimate. The respecified base case presented to the PBAC previously (para 6.58, nivolumab PSD, July 2022 PBAC meeting) applied higher values. |
| Treatment of distant recurrence | As the listing of nivolumab may affect the use of avelumab in distant recurrence, different post-recurrence costs and outcomes were applied across model arms. Survival outcomes following avelumab were based on Powles et al. (2023)15 and were adjusted for an assumed cure portion of 10%. The adjusted estimates are highly uncertain, as the proportion who achieved a cure in Powles et al. (2023) is unknown. Adjustment of these data is not a conservative approach. The cost per course was based on the mean treatment duration cited in the avelumab PSD (para 4.1, avelumab PSD, March 2022 PBAC meeting). The evaluation considered that this may be an overestimate as this was the duration which applied before the implementation of a financial stopping rule (where doses administered beyond some point would be provided at no cost).  |

Source: Table 35, p97 and Section 3 of the resubmission.

AE = adverse event; DFS = disease free survival; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; LY = life years; MIUC = muscle invasive urothelial cancer; NAC = neoadjuvant platinum-based chemotherapy; OS = overall survival; QALYs = quality-adjusted life years.

Blue shading indicates information previously seen by the PBAC.

* 1. The ESC noted the key changes in the model presented in the resubmission included:
* restricting the patient population to those who had received prior NAC;
* separation of the post-recurrence health state into locoregional and distant recurrence health states; and
* application of costs and outcomes for avelumab maintenance treatment of distant recurrence in the watchful waiting arm of the model only.
	1. Restricting the population to those who had received prior NAC and separation of the post-recurrence health states were revisions consistent with advice previously provided by the PBAC (paragraph 7.11, nivolumab PSD, July 2022 PBAC meeting). The PSD also noted that avelumab was recently recommended in the first-line maintenance setting and that immunotherapy is typically restricted to one regimen for a patient’s entire treatment course (paragraph 6.15, nivolumab PSD, July 2022 PBAC meeting), and so this is also a reasonable change.
	2. The PBAC previously requested that uncertainties raised during the evaluation and by the ESC be addressed, noting that the respecified base case did address some of these concerns (paragraph 7.9 and 7.11, nivolumab PSD, July 2022 PBAC meeting). The evaluator respecified base case of the previous submission used the best-fitting parametric model to independently extrapolate DFS; extended the KM truncation to 42 months (which was considered appropriate based on a sufficient number of patients [10% of the cohort] remaining at-risk; paragraph 6.47, nivolumab PSD, July 2022 PBAC meeting); excluded the assumption of a cure (as this was captured with the best-fitting extrapolations) and maintained the increased risk for all-cause mortality for the entire model duration (paragraph 6.58, nivolumab PSD, July 2022 PBAC meeting). The PBAC previously considered that more conservative assumptions regarding time horizon may reduce residual uncertainty in the respecified analyses (paragraph 7.9, nivolumab PSD, July 2022 PBAC meeting). The resubmission approached the previously raised concerns as follows:
* The 20-year time horizon presented previously was maintained based on the claim that uncertainties in the modelled estimates were reduced given the additional follow-up provided from the prior NAC subgroup of CM274. Additional data were provided only for DFS – no OS data were included in the resubmission. Modelled outcomes were therefore based on a number of assumptions (regarding how to account for cured patients; the duration and magnitude of the increased all-cause mortality; and survival following recurrence) and are likely to remain associated with a high degree of uncertainty. The incremental cost-effectiveness ratio (ICER) was moderately sensitive to the time horizon chosen. The PSCR stated that a 20-year time horizon is appropriate for nivolumab in this indication. It reiterated that with additional data available compared to the original submission, there is ‘minimal extrapolation and a high level of structural reliability in the model which supports this time horizon’. The PSCR argued that the cure fraction applied to the model means that there are a proportion of patients in both treatment arms who achieve cure, and these patients experience long-term survival. Therefore, to shorten the time horizon within the model would underestimate the cost and outcomes. The ESC disagreed with the PSCR noting a large percentage (79%) of incremental QALYs gained accrued in the economic model during the extrapolation. Noting the uncertainty in the economic model, the ESC considered a 15 year time horizon would be more appropriate.
* The increased risk in all-cause mortality was changed from 1.5x to 1.8x based on updated data from the prior NAC subgroup of CM274 and was applied for up to five years (compared to two years previously). No justification was provided for limiting the duration of increased risk. The ICER was moderately sensitive to changes in the duration of the increased risk applied. The PSCR argued that trial data (Sternberg et al., 2015) and Australian clinical practice are supportive of limiting the increased risk of all-cause mortality. However, it acknowledged the concerns held by the evaluation, and considered utilisation of a 1.1x multiplier for patients between 5 years and the end of the model would be reasonable. This change was stated to increase the ICER to $25,000 to < $35,000 per QALY gained. The ESC agreed with the published literature[[18]](#footnote-19),[[19]](#footnote-20) that suggests bladder cancer patients have an ongoing and moderately increased risk of death due to other causes, and therefore maintaining an increased risk of 1.8x for the duration of the model would be more appropriate.
* The probability of remaining in the pre-recurrence state was informed by observed and extrapolated DFS data from the prior NAC subgroup of CM274. DFS was extrapolated from 54 months. At this timepoint, approximately 12% (n = 20) and 7% (n = 11) of patients remained at risk of a DFS event in the nivolumab and placebo arms, respectively, of the prior NAC subgroup in CM274. The ICER is sensitive to the truncation point chosen for extrapolation of the DFS curve in the placebo arm of the prior NAC subgroup in CM274. The PSCR stated that a truncation point of 54 months for both treatment arms was selected on the basis that at this timepoint reflects approximately 10% of patients in the cohort remaining at risk. The PSCR argued that to vary the truncation point in only one treatment arm would be selective and inappropriate, and has a disproportionate impact on the ICER, favouring placebo. Therefore, the Sponsor maintained that 54 months remains an appropriate timepoint for truncation. The ESC considered that for extrapolation of placebo DFS, the truncation point used may be too late as there were fewer than 10% of patients remaining at risk. Reducing the truncation point in the placebo arm to 48 months (where 12% remain at risk, n = 19) may be a more appropriate choice.
* Independent Gompertz models were chosen for extrapolation. While this was the best fit for extrapolation of DFS following placebo, this was not the best fitting model for extrapolation of DFS for nivolumab. However, under the base case assumption where a cure was implemented after five years, the choice of parametric function for extrapolation of DFS for nivolumab has only a minor impact on the ICER. The ESC considered that while a Gompertz model was previously considered appropriate for extrapolation of DFS, this was in the context of the ITT population and at an earlier data cutoff and noted that it is no longer the best fitting model for the extrapolation of DFS for nivolumab.
* The model retained the cure assumption at five years. A cure assumption at five years in MIUC was considered likely reasonable by the PBAC (paragraph 6.49, nivolumab PSD, July 2022 PBAC meeting), however was excluded from the respecified base case previously as the best fitting models were able to capture a proportion of patients who achieved a cure. As Gompertz models were chosen in the resubmission’s updated base case analysis, cured patients may also be captured in these extrapolations (Figure 4). The PSCR argued that the Gompertz distribution used for the base case has a decreasing hazard over time, consistent with the clinical expectation that most recurrences occur soon after surgery. The ESC considered that implementation of a cure fraction at 5 years was reasonable but that the best fitting model (generalised gamma) should be used to extrapolate DFS in the nivolumab arm.

Figure 4: Comparison of independently fitted parametric functions used for DFS extrapolation



Source: Constructed during the evaluation from the ‘Attachment 14 - Nivolumab Adj MIUC Economic Evaluation\_Resubmission.xlsm’ file included in the resubmission.

\* Denotes parametric model which had best fit by Akaike information criterion and Bayesian information criterion

^ Denotes parametric model chosen in the base case analysis

DFS = disease-free survival; KM = Kaplan-Meier.

* 1. Other minor changes included in the evaluator respecified base case presented previously included increasing the disutility of AEs (based on Bregman 2020[[20]](#footnote-21), where available) and applying corrected chemotherapy pricing (based on the average rather than maximum dose and applying the cost of two chemotherapy administrations per treatment cycle, rather than one) (paragraph 6.58, nivolumab PSD, July 2022 PBAC meeting). While the resubmission had correctly applied the cost for the average dose of chemotherapy, the changes to the disutility values and the number of chemotherapy administrations were not adopted. This was not reasonable, however had negligible effect on the ICER (Table 16).
	2. As OS data were not provided in the resubmission, the model presented maintained a Markov model structure. This approach adds considerable uncertainty to the modelled estimates due to the assumptions required (including that DFS is a surrogate for OS and transitivity of the external studies used to inform survival with and without avelumab maintenance in distant recurrence). At the more recent data cutoff of September 2022, 64 deaths (41.0%) and 81 deaths (51.3%) had occurred in the nivolumab and placebo arms, respectively, in the prior NAC subgroup of CM274. The use of trial-based OS data directly in the model could reduce the reliance on these assumptions, or at least enable some validation of the modelled estimates. The PSCR stated that there is no trial-based OS data to inform the economic model and therefore the sponsor has selected the best available data to inform the model.
	3. The ESC noted that in the absence of OS data from CM274, survival after distant recurrence was modelled based on external studies.13,14,15 Bellmunt et al. (2012)13 and De Santis et al. (2012)14 were used in the previous submission to model outcomes following chemotherapy. The inclusion of data from Powles et al. (2023)15 was to allow modelling outcomes from avelumab maintenance treatment, which was assumed to apply in the comparator arm of the model alone. Substantial differences were noted across the patient characteristics in these external studies. Inferring differences in survival outcomes across these studies − and therefore the incremental benefit of avelumab − is highly uncertain. Furthermore, the survival outcomes from the external avelumab trial alone were adjusted to account for an assumed proportion of patients who achieved a cure (modelled separately). This adds additional uncertainty to the modelled estimates given that the proportion who achieved a cure in Powles et al. (2023) was unknown.
	4. Of the patients that received chemotherapy in the watchful waiting arm of the model, 63% were assumed to receive avelumab maintenance, based on expert opinion. In the avelumab PSD (March 2021 PBAC meeting), uptake was estimated to range from 65−95% of the 60−75% of patients expected to be free from progression after first-line chemotherapy; thus reflecting estimates in a range of 39−71% of avelumab use in those who had received prior chemotherapy. The ICER was sensitive to the proportion of patients expected to use avelumab maintenance treatment.
	5. The ESC also noted that expert opinion was used to determine the proportion of recurrence events that resulted in a cure (which varied by type of recurrence and model arm) (locoregional recurrence: 6.6% and 7.7%, nivolumab and watchful waiting, respectively; and distant recurrence: 2.7% and 4.2%, respectively).
	6. The ESC considered that the transition probabilities sourced from external studies13,14,15 and from expert opinion were highly uncertain.
	7. Costs of avelumab used in the economic model were based on an assumed effective price reflecting a 50% rebate on published pricing, with a mean duration of 12.64 months treatment assumed (paragraph 4.1, avelumab PSD, March 2022 PBAC meeting). The PSD for avelumab indicated that the PBAC accepted a financial stopping rule to manage the cost of avelumab treatment. This suggested that doses beyond such time would be provided at nil cost to the Commonwealth. The mean treatment duration when this rule was accounted for was noted in the PSD to be less than 12.64 months (paragraph 5.3, avelumab PSD, March 2022 PBAC meeting). Thus, the cost per treatment course for avelumab applied in the resubmission has been overestimated. The ESC noted that sensitivity analyses conducted during the evaluation which reduce the duration of avelumab treatment indicated that the ICER was sensitive to these changes.
	8. A comparison of the modelled DFS and OS curves to the DFS data from the trial are presented in Figure 5. This figure also depicts the effects on the resulting modelled DFS and OS estimates when the truncation time point for DFS extrapolation in the watchful waiting arm is reduced from 54 to 48 months and using the best-fitting parametric model for extrapolation of nivolumab DFS.

Figure 5: **Comparison of modelled DFS and OS versus observed DFS from CM274**



Source: Constructed during the evaluation from the ‘Attachment 14 - Nivolumab Adj MIUC Economic Evaluation\_Resubmission.xlsm’ file included in the resubmission.

DFS = disease-free survival; KM = Kaplan-Meier; OS = overall survival; WW = watchful waiting.

* 1. A summary of the key drivers of the model is presented in Table 12.

Table 12: **Key drivers of the model**

| Description | Method/Value | ImpactBase case: 　|　1/QALY gained |
| --- | --- | --- |
| DFS data used in the model | CM274 prior NAC subgroup, September 2022 data cut.  | High, favours nivolumab. Using the CM274 ITT data (July 2021 data cut) increased the ICER to ||||2/QALY gained. |
| Avelumab costs and outcomes | The incremental benefit of avelumab treatment based on external studies13,14,15 was highly uncertain, due to differences in the patients enrolled.The incremental cost of avelumab is an overestimate as the treatment duration applied (12.64 months) includes the doses the sponsor intends to be provided at no cost under the ‘financial stopping rule’. | Moderate, favours nivolumab. When using the previous submission assumptions on treatments available in distant recurrence, the ICER increased to ||||3/QALY gained.  |
| Time horizon | 20 years | Moderate, favours nivolumab. Reducing the time horizon to 15 years increased the ICER to ||||3/QALY gained. |
| DFS KM truncation for watchful waiting arm | 54 months. This may be too late, as the observed data at this time point are unreliable; a truncation point of 48 months may be more appropriate. | Moderate, favours nivolumab. Reducing the truncation time point to 48 months increased the ICER to ||||3/QALY gained. |
| All-cause mortality multiplier | 1.8x applied for five years. The increased risk was based on a comparison of CM274 data (prior NAC subgroup) with general population mortality in US males aged 63.9. No justification was provided for the duration of the increased risk applied. | Moderate, favours nivolumab. Maintaining the increased risk throughout the model increased the ICER to ||||1/QALY gained.  |

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; ITT = intention-to-treat; KM = Kaplan-Meier; NAC = neoadjuvant platinum-based chemotherapy; QALYs = quality-adjusted life years.

*The redacted values correspond to the following ranges:*

*1 $25,000 to < $35,000*

*2 $95,000 to < $115,000*

*3 $35,000 to < $45,000*

* 1. Table 13 presents a stepped incorporation of the changes in the resubmission to the ICER presented previously.

Table 13: **Stepped incorporation of changes relative to the previous submission**

| Step and component | Nivolumab | Watchful waiting | Increment |
| --- | --- | --- | --- |
| Step 1: Previous submission (July 2022 PBAC Meeting) base case |
| Costs  |  | | $28,398 |  | |
| QALYs | 4.410 | 3.679 | 0.731 |
| Incremental cost/extra QALY gained  |  |1 |
| Step 2: Restricting the population modelled to those who had prior NACThis step included changes to the demographics of the patients modelled, DFS data used (including truncation time point and parametric extrapolation), total mean cumulative dose of nivolumab, incidence of adverse events, utility weights, and updated assumptions on the background mortality multiplier and duration of higher risk applied. |
| Costs |  | | $28,572 |  | |
| QALYs | 5.135 | 3.506 | 1.629 |
| Incremental cost/extra QALY gained |  |2 |
| Step 3: Separate post-recurrence health state into locoregional and distant recurrence health statesThis step included structural changes whereby a proportion of recurrences (29%) were assumed to be locoregional and a proportion of recurrences (which varied by recurrence type and treatment arm) were assumed to achieve a cure (and were no longer at risk of further recurrences). Time in and subsequent transitions from the locoregional recurrence health state were based on PFS2 data in patients who experienced a local recurrence in CM274 (ITT population, Dec 2020 data-cut).  |
| Costs |  | | $30,877 |  | |
| QALYs | 5.347 | 3.881 | 1.466 |
| Incremental cost/extra QALY gained |  |2 |
| Step 4: Modelling costs and outcomes of avelumab maintenance treatmentOutcomes in the comparator arm of the model were adjusted to reflect avelumab use in 45% of patients who experienced a distant recurrence. This step also included minor changes to the distribution of carboplatin vs cisplatin use. Distant recurrence treatment costs were updated to include a wider range of treatments (predominantly avelumab in the comparator arm of the model, for which an assumed effective price was applied) |
| Costs |  | | $53,679 |  | |
| QALYs | 5.347 | 4.126 | 1.221 |
| Incremental cost/extra QALY gained |  |3 |
| Step 5: Other minor model updatesIncorporation of minor cost revisions such as updated cost of MBS items, AR-DRG codes and lifetables |
| Costs |  | | $55,233 |  | |
| QALYs | 5.369 | 4.142 | 1.227 |
| Incremental cost/extra QALY gained |  |3 |
| Step 6: Increase in the proposed effective price of nivolumab |
| Costs |  | | $55,233 |  | |
| QALYs | 5.369 | 4.142 | 1.227 |
| **Incremental cost/extra QALY gained (resubmission’s base case)** |  **|**4 |

Source: Analyses performed during the evaluation from the ‘Attachment 14 - Nivolumab Adj MIUC Economic Evaluation\_Resubmission.xlsm’ file included in the resubmission and the ‘Attachment 12 - Nivolumab Adj MIUC Economic Evaluation.xlsm’ file included in the previous submission.

DFS = disease free survival; ITT = intention-to-treat; NAC = neoadjuvant platinum-based chemotherapy; PFS2 = progression-free survival 2; QALYs = quality-adjusted life years.

*The redacted values correspond to the following ranges:*

*1 $35,000 to < $45,000*

*2 $15,000 to < $25,000*

*3 $0 to < $5,000*

*4 $25,000 to < $35,000*

* 1. The ESC noted that restricting the population modelled to those who had received prior NAC and including costs and outcomes of avelumab in the comparator arm of the model alone each led to substantial reductions in the ICER. In July 2022, the PBAC considered that an ICER of up to $30,000 per QALY gained would be consistent with previous PBAC decisions in the adjuvant therapy setting (paragraph 7.9, nivolumab PSD, July 2022 PBAC meeting). The ESC noted that the effective price for nivolumab was increased to the greatest extent with maintaining an ICER below $25,000 to < $35,000 per QALY gained. The ICER calculated was not based on the effective price of avelumab (or treatment duration when the financial stopping rule was included) as this information is not published.
	2. A comparison of the DFS estimates in the current and previous submission are presented in Figure 6. While the restriction in the population modelled is consistent with the proposed PBS listing, if there is substantial use in patients that do not reflect the population included in the prior NAC subgroup of the trial (such as in those who would not otherwise have received NAC – as estimated in the financial impact), then the cost-effectiveness claimed (and so justification for the higher proposed price) may not be realised in practice.

Figure 6: **Comparison of modelled DFS from the current and previous submission**



Source: Constructed during the evaluation from the ‘Attachment 14 - Nivolumab Adj MIUC Economic Evaluation\_Resubmission.xlsm’ file included in the resubmission

DFS = disease-free survival; ITT = intention-to-treat; WW = watchful waiting.

* 1. Disaggregated costs and outcomes are presented in Table 14.

Table 14: **Disaggregated costs and outcomes included in the economic evaluation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Nivolumab | Watchful waiting | Increment | % |
| **Costs ($)** |  |  |  |  |
| Nivolumab |  | | $0 |  | |  |% |
| Administration | $1,016 | $0 | $1,016 |  |% |
| Disease monitoring | $2,306 | $0 | $2,306 |  |% |
| Disease management (pre-recurrence)  | $2,317 | $1,774 | $542 |  |% |
| Treatment and disease management (post-recurrence) | $8,114 | $33,439 | −$25,325 | − |% |
| End of life care | $16,520 | $19,691 | −$3,171 | − |% |
| Adverse event related costs | $985 | $328 | $657 |  |% |
| **Total costs** |  **|** | **$55,232** |  **|** | **100%** |
| **QALYs** |  |  |  |  |
| Pre-recurrence | 4.812 | 3.150 | 1.662 | 135% |
| Locoregional recurrence | 0.153 | 0.204 | −0.052 | −4% |
| Distant recurrence | 0.407 | 0.789 | −0.382 | −31% |
| **Total QALYs** | **5.372** | **4.143** | **1.229** | **100%** |

Source: Compiled during the evaluation, based on the ‘Attachment 14 – Nivolumab Adjuvant MIUC Economic Evaluation’ Excel workbook.

QALYs = quality-adjusted life years

* 1. The main driver of the incremental cost is that of nivolumab acquisition, with substantial cost offsets from treatment and disease management in post-recurrence (driven by the cost of avelumab) and to a lesser degree, end of life care. As the treatment course cost of avelumab may be an overestimate, the incremental cost of nivolumab may be underestimated.
	2. Incremental QALYs gained were all accrued in the pre-recurrence health state, though a reduction in QALYs gained in distant recurrence was also observed (reflecting both fewer instances of distant recurrence and poorer survival outcomes). Substantial differences were noted across the external studies used to inform survival (and thus the incremental benefit of avelumab) in the metastatic setting. Therefore, the incremental benefit of avelumab modelled is highly uncertain. Furthermore, the survival outcomes from the external avelumab trial were adjusted for an assumed proportion of patients who achieved a cure. This adds additional uncertainty to the modelled estimates as the proportion who achieved a cure in Powles et al. (2023) was unknown. Given that the incremental benefit of avelumab is a major driver of the incremental QALYs gained, and that this is associated with considerable uncertainty, the resulting ICER is also highly uncertain.
	3. 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 trial.

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

|  | **CheckMate274 (prior NAC subgroup)****(median follow-up: 36.1 months)** | **Economic model****(time horizon of 20 years)** |
| --- | --- | --- |
| **Nivolumab (n=156)** | **Placebo (n=158)** | **Difference** | **Nivolumab** | **Watchful waiting** | **Difference** |
| Recurrence events | 46%a | 65%a | −18.40% | 60%b | 81%c | −20.97% |
| Deaths | 41%d | 51%d | −7.94% | 71%e | 83%f | −11.24% |
| Life years (undiscounted) | 2.479g | 2.322g | 0.157 | 9.282h | 6.96h | 2.321 |

Source: Table compiled during the evaluation, based on the economic workbook provided with the resubmission

DFS = disease free survival; NAC = neoadjuvant platinum-based chemotherapy

a Calculated by subtracting pre-recurrence deaths from number of patients with a DFS event in each arm. Pre-recurrence deaths are 7 and 11 and total DFS events are 82 and 113 nivolumab and placebo arm respectively. Recurrence events are 72 and 102 in nivolumab and placebo arms respectively.

b Sum AD101:AE199 in ‘Model’ tab of economic workbook provided with the resubmission.

c Sum AR101:AR129 in ‘Model’ tab of economic workbook provided with the resubmission.

d In the prior neoadjuvant platinum-based chemotherapy subgroup, at the time of the September 2022 data cutoff, 64 deaths (41.0%) and 81 deaths (51.3%) had occurred in the nivolumab and placebo arms, respectively (updated CM274 data report, Attachment 8 accompanying the resubmission).

e Cell AB189 in ‘Model’ tab of economic workbook provided with the resubmission.

f Cell AY189 in ‘Model’ tab of economic workbook provided with the resubmission.

g After setting time horizon to medial follow-up (36.1 months) and discount rate to 0%

h After setting time horizon to 20 years and discount rate to 0%.

* 1. The proportion of patients experiencing recurrence in the nivolumab arm increased from 46% in CM274 to 60% in the model. The corresponding recurrence results in the comparator arm were 65% in the trial versus 81% 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 only recurrences that occurred after 5 years were from locoregional to distant metastasis. The proportion of patients who died increased from 41% to 71% in the nivolumab arm and from 51% to 83% in the comparator 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 0.157 during the trial period to an extrapolated 2.321 at Year 20. For every 1,000 patients treated with adjuvant nivolumab and followed-up for 20 years, the economic model estimated (undiscounted) that there would be:
* nivolumab drug cost of $| | million;
* 210 recurrence events avoided;
* 112 deaths avoided; and
* 2,321 LYG.
	1. The results of key univariate sensitivity analyses are summarised in Table 16.

Table 16: **Results of key sensitivity analyses**

|  | Inc. cost ($) | Inc. QALYs | ICER | % change from base case |
| --- | --- | --- | --- | --- |
| **Base case** |  **||** | **1.227** |  **||**1 |  |
| Discount rate (base case: 5%) |  |  |  |  |
| * 0%
 |  || | 1.963 |  　|　2 | − 　|　 |
| * 3.5%
 |  || | 1.400 |  　|　1 | − 　|　 |
| Time horizon (base case: 20 years) |  |  |  |  |
| * 15 years **(#5)**
 |  || | 1.002 |  　|　3 |  | |
| * 17.5 years
 |  || | 1.126 |  　|　1 |  | |
| DFS data used (base case: prior NAC subgroup), ITT |  || | 0.382 |  　|　4 |  | |
| Placebo KM DFS truncation, 48 months (base case: 54 months) **(#1)** |  || | 1.072 |  　|　3 |  | |
| DFS extrapolation (base case: both Gompertz) |  |  |  |  |
| * Both Generalised gamma
 |  || | 1.258 |  　|　1 | − 　|　 |
| * nivolumab by Generalised Gamma, placebo by Gompertz **(#3)**
 |  || | 1.200 |  　|　1 |  | |
| Cure assumptions, none (base case: 5 years) |  || | 1.202 |  　|　1 |  | |
| Duration of increased mortality risk, lifetime (base case: 5 years) **(#2)** |  || | 1.137 |  　|　1 |  | |
| Distribution of recurrences (base case: 29% locoregional) |  |  |  |  |
| * All locoregional
 |  || | 1.288 |  　|　3 |  | |
| * None locoregional
 |  || | 1.202 |  　|　1 | − 　|　 |
| Cure rate in distant recurrence (base case: NIVO 2.7%, WW 4.2%) |
| * 0% NIVO, 5% WW
 |  || | 1.110 |  　|　1 |  | |
| * No cure
 |  || | 1.314 |  　|　1 | − 　|　 |
| Distant recurrence mean survival following NIVO (base case: 16.3 months) |
| * 1.5x increase
 |  || | 1.401 |  　|　1 | − 　|　 |
| * 1.5x decrease
 |  || | 1.105 |  　|　1 |  | |
| Distant recurrence mean survival following WW (base case: 24.9 months) |
| * 1.5x increase
 |  || | 0.897 |  　|　3 |  | |
| * 1.5x decrease
 |  || | 1.465 |  　|　1 | − 　|　 |
| Utility values (base case: prior NAC 3 level) (pre-recurrence: 0.820, LR: 0.700, DR: 0.731) |
| * ITT (3 level): pre-recurrence: 0.830, LR: 0.746, DR: 0.727
 |  || | 1.246 |  　|　1 | − 　|　 |
| * Pre-recurrence: 0.780, post-recurrence: 0.634 a
 |  || | 1.201 |  　|　1 |  | |
| Disutility values, from Bregman (2020)b where available **(#4)** |  || | 1.225 |  　|　1 |  | |
| No. administrations per chemotherapy cycle, 2 (base case: 1) c **(#4)** |  || | 1.227 |  　|　1 | − 　|　 |
| Exclude costs and outcomes of avelumab maintenance |  || | 1.473 |  　|　3 |  | |
| Applying consistent proportions of avelumab use in the costs and outcomes of treating distant metastasis d **(#7)** |  || | 1.240 |  　|　1 | − 　|　 |
| Avelumab treatment duration (base case: 12.6 months) |  |  |  |  |
| * 8 months
 |  || | 1.227 |  　|　3 |  | |
| * 10 months **(#6)**
 |  || | 1.227 |  　|　1 |  | |
| Proportion of patients who receive avelumab maintenance after chemotherapy (base case: 63%) |
| * 39%
 |  || | 1.319 |  　|　1 |  | |
| * 71%
 |  || | 1.197 |  　|　1 | − 　|　 |
| **Multivariate analyses** |  |  |  |  |
| #1 AND #2 |  || | 0.997 |  　|　3 |  | |
| #1, #2 AND #3 |  || | 0.973 |  　|　3 |  | |
| #1, #2, #3 AND #4 |  || | 0.971 |  　|　3 |  | |
| #1, #2, #3, #4 AND #5 |  || | 0.829 |  　|　5 |  | |
| #1, #2, #3, #4, #5 AND #6 |  || | 0.829 |  　|　5 |  | |
| **Re-specified base case: #1, #2, #3, #4, #5, #6 AND #7**  |  **||** | **0.842** |  **||**5 |  **|** |

Source: Compiled during the evaluation, based on Table 80 and the ‘Attachment 14 – Nivolumab Adjuvant MIUC Economic Evaluation’ Excel workbook.

DFS = disease free survival; DR = distant recurrence; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; KM = Kaplan-Meier; LR = locoregional recurrence; NAC = neoadjuvant platinum-based chemotherapy; NIVO = nivolumab; QALY = quality adjusted life year; WW = watchful waiting.

a Analysis presented in sensitivity analyses previously (Table 16, nivolumab PSD, July 2022 PBAC meeting)

b Bregman B, Teitsson S, Orsini I, Cotté F-E, Amadi A, Moshyk A, et al. Cost–Utility Analysis of Nivolumab in Adjuvant Treatment of Melanoma in France. Dermatology and Therapy. 2020 2020/12/01;10(6):1331-43.

c As gemcitabine is administered in days 1 and 8 per treatment cycle, two services of MBS item 13950 should be applied per treatment cycle, rather than one, as assumed in the resubmission base case analysis.

d The base case assumed that 42.5% of patients experiencing a distant metastasis would incur the cost of avelumab use, however outcomes were modelled assuming avelumab use in 45.0% of patients experiencing a distant metastasis. As experts advised (Attachment 3 to the resubmission) 42.5% avelumab use in distant metastasis, the approach to model outcomes has been adjusted for consistency in this sensitivity analysis.

*The redacted values correspond to the following ranges:*

*1 $25,000 to < $35,000*

*2 $15,000 to < $25,000*

*3 $35,000 to < $45,000*

*4 $95,000 to < $115,000*

*5 $45,000 to < $55,000*

* 1. The analyses were most sensitive to assumptions related to cost and outcomes of avelumab maintenance treatment. As described above, the use and cost of avelumab treatment are likely to be overestimated, and due to transitivity issues between the external studies used to inform survival after disease recurrence, the incremental benefit of avelumab modelled is highly uncertain. The analysis was also sensitive to reductions in the time horizon, changing the truncation time point for watchful waiting DFS, and extending the increased all-cause mortality risk throughout the model time horizon.
	2. Multivariate analyses were conducted during the evaluation around these key areas of uncertainty identified, including changes made in the respecified base case presented previously or other concerns raised by the PBAC (paragraph 7.9, nivolumab PSD, July 2022 PBAC Meeting).
	3. The ESC considered that resubmission’s base case remained underestimated. The ESC considered this was primarily due to concerns regarding the: time horizon; DFS extrapolation function applied; truncation time point for watchful waiting DFS; duration of increased mortality risk; and avelumab treatment duration (see paragraphs 6.57 and 6.63). The ESC noted that the ICER is sensitive to cumulative changes in the model and considered that the multivariate analysis conducted during the evaluation resulting in an ICER of $45,000 to < $55,000 per QALY gained would be more appropriate. However, the ESC also considered that due to the lack of provision of OS data, the results remain uncertain. The ESC considered the 113% increase in the requested price from $| | in the March 2023 submission to $| | per vial on the basis of restricting the population modelled to those who had received prior NAC and including costs and outcomes of avelumab in the comparator arm was not justified given:
1. the proposed restriction will allow patients not receiving, or receiving minimal NAC, to access nivolumab. The ESC considered even if the criteria allowing use in patients with contraindications/intolerance to NAC is removed from the restriction, the efficacy observed in clinical practice is likely to be less than observed in the trial subgroup;
2. the ICER is less reliable given it is based on a subgroup of the trial patients;
3. lack of clinical data supporting the claim of an increase in OS; and
4. the underestimation of the base case ICER in the submission.
	1. The pre-PBAC response disagreed with the ESC assessment that the resubmission’s base case remained underestimated. In addition, the pre-PBAC response argued that, while it was likely that additional patients will be treated with NAC compared to current rates, the CM274 trial represented the best available evidence for the efficacy of nivolumab as adjuvant treatment for MIUC in NAC treated patients. The pre-PBAC response also noted the selection of a trial subgroup was based directly on advice from the PBAC in its July 2022 consideration of nivolumab and argued the resubmission ICER may be more reliable given the granularity in health states and additional follow-up provided in the model. Finally, the pre-PBAC response argued that the economic model does not directly claim increased OS for patients receiving nivolumab with time spent by patients in the pre-recurrence state instead informed through direct evidence of DFS from CM274.

Drug cost/patient/course

* 1. The per patient cost of nivolumab used in the model and the financial analysis, is presented in Table 17. As all patients who had received prior NAC in CM274 had discontinued treatment at the time of the latest data cut, the cumulative average dose received in the trial was applied directly in the economic analysis and financial impact, assuming that patients would receive the recommended dose each cycle. While the total dose applied was consistent across the analyses, due to different assumptions in dosing regimen applied, slight differences were observed.
	2. Due to the proposed increase in the effective price, the cost per patient estimated was substantially higher than in the previous submission (approximately $| |).

Table 17: **Drug cost per patient for nivolumab**

|  | Trial dose and duration | Model | Financial estimates |
| --- | --- | --- | --- |
| Total cumulative mean dose (dosing regimen) | 4,272 mg(240mg Q2W) | 4,272 mg(480mg Q4W) | 4,272 mg(10% 240mg Q2W; 90% 480mg Q4W) |
| Mean no. cycles | 17.80 cyclesa | 8.90 cyclesa | 240mg Q2W: 17.86 cyclesa480mg Q4W: 8.93 cyclesa |
| Cost/patient/cycle ($) |  |b |  |b | 240mg Q2W: 　|　b, 480mg Q4W: |b |
| Cost/patient/course ($) |  | |  | |  | |

Source: Table constructed during the evaluation

Q2W = every 2 weeks; Q4W = every 4 weeks

a Derived from total cumulative mean dose divided by dose (e.g. 4,272 ÷ 240 mg = 17.8)

b Assuming 33.86% of the nivolumab scripts will be dispensed in a public hospital setting, and 66.24% in a private hospital setting.

Estimated PBS usage & financial implications

* 1. This resubmission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the expected utilisation and financial impacts associated with the proposed PBS listing of nivolumab. This approach is unchanged from the previous submission and was reasonable.
	2. The PBAC previously considered the financial estimates presented in the previous submission were high and potentially underestimated. Concerns were noted relating to the incidence growth rate assumed, the percentage of patients at high-risk of recurrence, and the assumed rate of nivolumab uptake (paragraph 7.10, nivolumab PSD, July 2022 PBAC meeting). While the uptake rate of nivolumab was updated in the resubmission, inputs related to the incidence growth rate and proportion of patients at high-risk of recurrence were unchanged.
	3. Changes included in the resubmission to estimate the financial impact are:
1. restricting treatment to patients who have received prior NAC;
2. avelumab cost offsets in metastatic patients;
3. inclusion of prevalent pool of patients in Year 1;
4. increase in the uptake of nivolumab to 90%; and
5. increase in the uptake of prior NAC due to listing of nivolumab.
	1. 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: **Key inputs for financial estimates**

| Parameter | Value applied and source | Comment |
| --- | --- | --- |
| Incident cases of bladder, ureter or renal pelvis cancer (T1-T4) | Incident cases reported by the AIHW in 2021 (bladder) and 2016 (ureter and renal pelvis cancer) were projected using Australian population growth estimates published by the ABS to 2024−29 estimates. | This was not reasonable as the AIHW have published incidence projections for bladder cancer and cancer of other urinary organs to 2031. a |
| Incident cases of bladder, ureter or renal pelvis cancer (Ta and Tis) | Assuming 55.9% of all urothelial cases in Australia (Reynolds et al. 2021)b are Ta and Tis, incident cases were derived from the estimated incident T1-T4 cases. | This was unchanged from the previous submission and was reasonable. |
| Proportion with urothelial carcinoma | 89% of bladder cancer and 93.5% of ureter or renal pelvis cancer, based on AIHW estimates (personal communication). 2% of patients were excluded due to possible double counting, based on the estimates from the BLADDA registry. c | This was unchanged from the previous submission and was reasonable. |
| Proportion of T1-T4 who have MIUC at diagnosis | 53.5% (Reynolds et al. 2021) b | This was unchanged from the previous submission and was reasonable. |
| Proportion of NMIUC who progress to MIUC | 12% (BLADDA registry) c | Minor changes were applied to these estimates from those used previously, based on updated data from BLADDA. c These were reasonable. |
| Proportion of MIUC with radical resection | 64.1% (BLADDA registry) c |
| Proportion of patients with WHO PS 0 or 1 | 97% (BLADDA registry) c |
| Proportion of patients who receive prior NAC | Without nivolumab listing this was assumed to be 44.2%, based on use in the CM274 trial. Following nivolumab listing, this was assumed to increase to 50.8% in Year 1 to 67.4% by Year 6 based on clinical opinion. | The responses provided by clinicians were quite variable. The estimates applied were therefore highly uncertain. |
| Risk of recurrence after radical surgery | 50% based on a Pre-Advisory Board survey | This was unchanged in the resubmission and may not be reasonable (para 7.10, nivolumab PSD, July 2022 PBAC meeting). |
| Uptake of nivolumab | Assumed to be 90% based on the claim that patients would be treated with NAC with the intent to progress to adjuvant nivolumab | This was increased from 57% assumed previously and is uncertain. |
| Prevalent patients | 56% of incident cases in Year 1, based on the time interval from diagnosis to commencement of adjuvant therapy (approx. 204 days) | It is unclear whether patients would delay surgery in anticipation of nivolumab listing. |
| Nivolumab dose | Cumulative mean total dose was 4,272 mg, based on use in the prior NAC subgroup of CM274. Assuming that patients would receive the recommended dose each cycle, this was equivalent to 17.8 Q2W and 8.9 Q4W doses | Nivolumab dosing was updated to reflect use in the prior NAC subgroup of CM274. This was reasonable. |
| Relative use of nivolumab Q2W vs Q4W  | Q2W: 10%, Q4W: 90% based on previous PBAC advice (para 5.4, nivolumab PSD, March 2019 PBAC meeting) | This was unchanged from the previous submission and was reasonable. |
| Proportion of patients who would develop distant recurrence in the absence of nivolumab | Output from the watchful waiting arm of the economic model on the incidence of distant recurrence | While the source was reasonable, these data were incorrectly applied d and resulted in an underestimate of the number of patients with distant recurrence from Year 2 onwards. |
| Use of avelumab in distant recurrence | Assumed in 80% of patients who would otherwise have developed distant recurrence. | This was higher than applied in the economic model (43% of distant recurrences) and is likely an overestimate. |
| Administration of antineoplastic agent | $114.20 based on MBS item 13950 | This was reasonable. |

Source: Table 83, p161-163 of the resubmission

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

a Australian Institute of Health Welfare. Cancer in Australia 2021. Canberra: AIHW 2021. Report No.: Cancer series no. 133. Cat. no. CAN 144.

b Reynolds BR, McCombie S, Botha E, Hawks C, Brown M, Hayne D. Ten-year outcomes of the first ‘one-stop haematuria clinic’ in an Australian public hospital. ANZ Journal of Surgery. 2021;91(4):565-70.

c Tran, B. (2023). BLADDA - Bladder and Urothelial Cancer Data and Biobank, Data Report.

d Model output related to the incidence of distant recurrence for an average patient over the first six years from model entry, however the resubmission applied these estimates to cohorts over time, rather than for each cohort e.g. distant recurrences for patients treated in Year 1 were assumed only within that first year, incidence in the second year was applied to patients treated in Year 2.

* 1. In its July 2022 meeting, the PBAC noted concerns regarding the growth rate used to estimate the number of incident cancer cases (paragraph 7.10, nivolumab PSD, July 2022 PBAC meeting). The resubmission has not changed the approach used to estimate incident cases. This was not reasonable given that the AIHW have published incidence projections to 2031.[[21]](#footnote-22) These estimates are higher than those applied in the resubmission and may be a more appropriate basis for the financial estimates.
	2. The PSCR provided a revised net cost to the PBS/RPBS. The PSCR stated the updated financial estimates were based on the AIHW incidence projections, a 10 month stopping rule for avelumab and a percentage of patients with distant recurrence to receive avelumab consistent with the economic model (43%). However, the PSCR applied updated AIHW estimates for bladder cancer but not the updated projections published by the AIHW for other urinary organs. Further, the PSCR revised estimates did not address the error identified in the commentary regarding how distant recurrences have been estimated in Years 2 onwards and therefore the incidence of distant recurrences in Years 2 onwards remains underestimated.
	3. As the proposed population is restricted to those who have received prior NAC, the resubmission estimated the usage of prior NAC and the impact of nivolumab listing on uptake of prior NAC from clinical expert feedback. Based on this, it was estimated that uptake of prior NAC would increase from 50.83% in Year 1 to 67.38% in Year 6. The clinical experts provided highly varied responses, ranging from estimated uptake in Year 1 from 20% to 80%; and in Year 5 from 30% to 80%. Therefore, the estimated use of prior NAC is highly uncertain.
	4. Following radical resection, the proportion assumed to be at high risk of recurrence (50%) was unchanged and so remained based on advice provided by the sponsor held Genitourinary Advisory Board meeting with medical oncologists and urologists. The ESC previously considered that this assumption was not reasonable and resulted in uncertainty in the number of eligible patients and the cost of nivolumab adjuvant treatment (paragraph 6.69, nivolumab PSD, July 2022 PBAC meeting). Sensitivity analyses presented observed that a 10% change in the proportion of patients at high-risk resulted in 20% change in the net cost to PBS/RPBS (Table 20).
	5. A prevalent pool of patients was included for the first year of listing in the resubmission based on the time interval from diagnosis to commencement of adjuvant therapy. Time to treatment initiation with adjuvant nivolumab was estimated to be 204 days after diagnosis. This was based on maximum duration of neoadjuvant chemotherapy (84 days) and the proposed restriction criteria for treatment initiation with nivolumab after surgery (120 days). As 204 days equates to 56% of a calendar year, an additional prevalent pool of patients (56% of incident cases in year 1) was estimated. It is unclear whether patients would delay surgery in anticipation of nivolumab listing, reducing the prevalent pool to 33% of incident cases, based on a delay up to 120 days after surgery, may be reasonable.
	6. The resubmission increased the uptake of nivolumab from 57% in the previous submission to 90%. The sponsor justified the high uptake of nivolumab stating that patients are treated with neoadjuvant chemotherapy prior to surgery with the intent to progress to adjuvant nivolumab. The estimated uptake is highly uncertain. Given the increased uptake of NAC and that the resubmission claimed the intent of use NAC is with the intent to treat with adjuvant nivolumab, it is unclear whether patients expected to uptake nivolumab in practice would reflect those patients in the prior-NAC subgroup of CM274, and such use may not be cost-effective. The proportion of patients in CM274 who used prior NAC was 44.2%. The ESC recalled it had previously considered a rate of uptake of 57% was likely to be underestimate, and considered that 80% may be a more reasonable estimate of uptake. The pre-PBAC response stated that an uptake of 90% was reasonable for patients who have received prior NAC as adjuvant nivolumab is the only treatment referred to in the NCCN guidelines. As such, the pre-PBAC response considered it unlikely that in Australian clinical practice clinicians would withhold therapy for 1 in 5 patients.
	7. The listing of adjuvant nivolumab was expected to impact the use and cost of avelumab therapy following recurrence and increase the cost of chemotherapy regimens due to the increased use of prior NAC. The resubmission did not consider that availability of nivolumab may also affect the use of medicines or monitoring requirements for AEs and the use of adjuvant therapy. Incidence of recurrence in the absence of nivolumab was derived from the placebo arm of the prior NAC subgroup of CM274 (where recurrences were observed over 5+ years). While this was reasonable, these data have been incorrectly applied – for example, the number of patients treated in Year 2 was multiplied by the incidence of distant recurrence in the second year following surgery. Therefore, underestimating the impact on changes in use and cost of avelumab treatment from Year 2 onwards. Of distant recurrence cases, 80% were assumed to have received treatment with avelumab. This was higher than applied in the economic evaluation (43%) and is likely to be an overestimate. As stated above, the PSCR provided updated financial estimates with a percentage of patients with distant recurrence receiving avelumab consistent with the economic model (43%), however the errors identified in the commentary were not addressed (see paragraph 6.87).
	8. The increase in use of prior NAC was calculated based on the difference between use in the trial (44.2%), so reflecting the proportion that would have had prior NAC in the absence of a nivolumab listing, and expected use of NAC following nivolumab listing, from expert opinion. These figures range from 6.64% in Year 1 to 23.18% in Year 6 as the proportion is expected to increase over time. As the uptakes rates from expert clinicians are likely uncertain, so too is the rate of increase and the financial impact. The ESC noted the use of prior NAC was assumed to increase with the listing of nivolumab. The ESC considered the use of nivolumab would be less cost-effectiveness in a broader population of patients treated with NAC (i.e. those previously not treated with NAC but now treated in order to access nivolumab).
	9. The estimated use and financial implications of nivolumab treatment is presented in Table 19.

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 a |  　|　1 |  　|　3 |  　|　3 |  　|　3 |  　|　3 |  　|　3 |
| Number of scripts dispensed a |  　|　2 |  　|　1 |  　|　1 |  　|　1 |  　|　1 |  　|　1 |
| Estimated financial implications of nivolumab |
| Cost to PBS/RPBS less co-payments | |4 | |5 | |5 | |5 | |5 | |5 |
| **Estimated financial implications for other medicines** |
| Cost to PBS/RPBS less co-payments |  　|　7 |  　|　7 |  　|　7 |  　|　7 |  　|　7 |  　|　7 |
| Revised b |  　|　7 |  　|　7 |  　|　7 |  　|　7 |  　|　7 |  　|　7 |
| Net financial implications |
| **Net cost to PBS/RPBS** |  **|**5 |  **|**5 |  **|**5 |  **|**5 |  **|**5 |  **|**5 |
| **Net cost to PBS/RPBS (revised)**  |  **|**5 |  **|**6 |  **|**6 |  **|**6 |  **|**6 |  **|**5 |
| Net cost to MBS |  　|　7 |  　|　7 |  　|　7 |  　|　8 |  　|　7 |  　|　8 |
| Net cost to Government |  　|　5 |  　|　5 |  　|　5 |  　|　5 |  　|　5 |  　|　5 |
| Revised |  　|　5 |  　|　6 |  　|　6 |  　|　6 |  　|　6 |  　|　5 |
| Previous submission (July 2022) |
| Number of patients treated |  　|　3 |  　|　3 |  　|　3 |  　|　3 |  　|　3 |  　|　3 |
| Number of scripts dispensed |  　|　1 |  　|　1  |  　|　1  |  　|　1 |  　|　1  |  　|　1  |
| **Net cost to PBS/RPBS** |  **|**6 |  **|**6 |  **|**6 |  **|**6 |  **|**6 |  **|**6 |

Note: Estimates were revised during the preparation of the ESC advice to correct the approach used to estimate incident distant recurrence patients and to assume 43% uptake of avelumab maintenance (as used in the economic evaluation).

Source: Compiled during the evaluation, based on financial workbook provided with the submission.

a The numbers were corrected during the evaluation as Table 85, p166 of the resubmission made typographic errors.

*The redacted values correspond to the following ranges:*

*1 500 to < 5,000*

*2 5,000 to < 10,000*

*3 < 500*

*4 $30 million to < $40 million*

*5 $20 million to < $30 million*

*6 $10 million to < $20 million*

*7 net cost saving*

*8 $0 to < $10 million*

* 1. The total cost to the PBS/RPBS of listing nivolumab was estimated in the resubmission to be $20 million to < $30 million (revised: $10 million to < $20 million) in Year 6, and a total of $100 million to < $200 million (revised: $100 million to < $200 million) in the first 6 years of listing. These were based on an assumed effective price for avelumab.
	2. The ESC noted that the net financial impact to the PBS/RPBS has increased relative to the previous submission, despite narrowing of the patient population eligible for treatment and including cost-offsets of avelumab maintenance use.
	3. It was noted during the evaluation that by Year 6, the estimated number of patients expected to uptake treatment with nivolumab was higher than Year 6 estimates previously. This is due to the increase in the proportion of patients who uptake NAC due to the listing of nivolumab and the higher rate of uptake assumed.
	4. The base case variables and parameters changed in the sensitivity analyses are presented in Table 20 around the revised impact to the PBS/RPBS. Results showed that the net PBS/RPBS implications were sensitive to the change in the proportion of patients at high risk of recurrence after radical resection, uptake rate of nivolumab and proportion of prior NAC usage.

**Table 20:** **Key sensitivity analyses around the financial impact of listing nivolumab**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **2024** | **2025** | **2026** | **2027** | **2028** | **2029** |
| **Net cost to the PBS/RPBS (revised)** | **|**1 | **|**2 | **|**2 | **|**2 | **|**2 | **|**1 |
| Incidence based on AIHW projections | |1 | |2 | |2 | |1 | |1 | |1 |
| Risk of recurrence, base case: 50% |
| 40% | |1 | |2 | |2 | |2 | |2 | |2 |
| 60% | | | |1 | |1 | |1 | |1 | |1 |
| Uptake of nivolumab, base case: 90% |
| 57% | |2 | |2 | |2 | |2 | |2 | |2 |
| 80% | |1 | |2 | |2 | |2 | |2 | |2 |
| Prior NAC use, base case: 50.8% in Year 1, increasing to 67.4% in Year 6 |
| 44.2% (i.e. no increase in NAC use with nivolumab listing) | |1 | |2 | |2 | |2 | |2 | |2 |
| Months of avelumab treatment, base case: 12.64 months |
| 8 months | |1 | |2 | |1 | |1 | |1 | |1 |
| 10 months | |1 | |2 | |2 | |1 | |1 | |1 |

Source: Compiled during the evaluation

NAC = neoadjuvant platinum-based chemotherapy.

*The redacted values correspond to the following ranges:*

*1 $20 million to < $30 million*

*2 $10 million to < $20 million*

Quality Use of Medicines

* 1. No changes have been made from the previous submission. The sponsor is committed to supporting the safe and effective use of nivolumab in Australia. Given the adverse effect profile of immune-oncology 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, amongst others, physician education, a risk management plan, educational materials, and guidance on monitoring and treating immune related adverse reactions.

Financial Management – Risk Sharing Arrangements

* 1. In its July 2022 meeting, the PBAC considered the financial estimates presented in the submission were high and potentially underestimated. At that time the PBAC suggested a 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 (paragraph 7.10, nivolumab PSD, July 2022). The sponsor did not propose a RSA but noted they are willing to enter a RSA.
	2. The ESC considered that even with the amendments suggested by the Committee to the proposed restriction (see paragraph 3.3) the use of prior NAC would likely increase with the listing of nivolumab. The ESC considered the use of nivolumab would be less cost-effectiveness in a broader population of patients treated with NAC (i.e. those previously not treated with NAC but now treated in order to access nivolumab). The ESC considered a RSA would likely be required to mitigate the uncertainty associated with use in a broader population of patients treated with NAC.

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

1. PBAC Outcome
	1. The PBAC deferred making a recommendation for nivolumab for the adjuvant treatment of high-risk muscle invasive urothelial carcinoma (MIUC) to allow for further consultation with the sponsor regarding a cost-effective price for nivolumab. The PBAC agreed with the ESC that despite the use of more reasonable inputs the incremental cost-effectiveness ratio (ICER) from the multivariate analysis remained uncertain. The PBAC considered a substantial price reduction would be required to achieve cost-effectiveness.
	2. The PBAC noted the input from health care professionals and organisations received for this resubmission and for the July 2022 meeting. The input across both submissions highlighted the impact of MIUC on health-related quality of life (HRQoL) and the potential benefit of nivolumab in reducing the risk of recurrence. The PBAC also noted the support for nivolumab for this indication from the Medical Oncology Group of Australia (MOGA).
	3. With regard to the requested restriction, the PBAC noted the pre-PBAC response argument that restricting access to the prior NAC treated population could create potential inequities in access for those who were unable to receive such prior treatment due to a contraindication. However, the PBAC considered that subgroup analysis from the CM274 trial indicated there was no clear disease free survival (DFS) benefit for patients with no prior use of NAC (September 2022 cut-off: Prior NAC use: HR = 0.54 [95% CI: 0.41, 0.72]; No prior NAC use: HR = 0.88 [95% CI: 0.68, 1.14]). The PBAC also considered that patients where NAC is contraindicated are typically unfit in other ways and hence would be least likely to benefit from nivolumab. In addition, the Committee considered the term ‘contraindication’ can often be interpreted very broadly. Overall, the PBAC considered there are significant cost and quality use of medicine issues arising from use in a patient population with no proven treatment benefit and advised the clinical criterion allowing use in patients who have a contraindication or intolerance to NAC be removed. The PBAC also reaffirmed its July 2022 advice that immunotherapy should be restricted to one course of treatment per lifetime given the paucity of clinical and economic evidence to support retreatment (paragraph 3.10, nivolumab, PSD, July 2022 PBAC meeting).
	4. The PBAC considered the comparator of watchful waiting was appropriate.
	5. The primary clinical evidence supporting the clinical claim remained the CM274 trial comparing adjuvant nivolumab with placebo in subjects with high risk invasive urothelial carcinoma. Consistent with the PBAC’s July 2022 advice the resubmission presented outcomes for the prior NAC subgroup (N = 314) of the CM274 trial and its complement. The PBAC considered the updated DFS data provided in the resubmission (September 2022 data cutoff) reaffirmed the Committee’s previous advice that no clear DFS benefit was observed with nivolumab over placebo in patients who had not received prior NAC (see paragraph 7.3). The PBAC noted the resubmission did not provide updated overall survival (OS) data for the September 2022 data cutoff (median duration of follow-up 36.1 months) stating that the data remain immature. The PBAC reiterated its July 2022 advice that longer-term OS data are required to determine whether the observed improvement in DFS translates into a clinically meaningful OS benefit (see paragraph 6.21). Overall, the PBAC considered the resubmission’s claim that adjuvant treatment with nivolumab in patients who have received prior NAC is superior in terms of effectiveness compared to placebo (as a proxy for watchful waiting) was reasonable for DFS.
	6. The PBAC reaffirmed its July 2022 advice that the claim of inferior comparative safety was reasonable (paragraph 7.7, nivolumab, PSD, July 2022 PBAC meeting).
	7. The PBAC noted the economic model presented in the resubmission included two main changes: (i) restricting the population only to those who had prior NAC; and (ii) the inclusion of costs and outcomes of avelumab maintenance treatment in the metastatic setting in the comparator arm of the model. These changes led to a substantial reduction in the ICER relative to that presented in the previous submission. The PBAC noted that the effective price for nivolumab was maximised to the greatest extent (more than double that proposed in July 2022) while maintaining an ICER below $25,000 to < $35,000 per QALY gained. The PBAC agreed with the ESC that the resubmission base case was underestimated primarily due to concerns regarding the: time horizon; DFS extrapolation function applied; truncation time point for watchful waiting DFS; duration of increased mortality risk; and avelumab treatment duration (see paragraphs 6.57 and 6.63). The PBAC noted the ICER increased from $25,000 to < $35,000 per QALY gained to $45,000 to < $55,000 per QALY gained when more reasonable inputs for these parameters were utilised in a multivariate analysis. Despite the use of more reasonable inputs, the PBAC considered the ICER from the multivariate analysis remained uncertain (see paragraph 6.78). The PBAC also noted that in the absence of OS data from CM274, survival after distant recurrence was modelled based on external studies, with the resulting incremental benefit of avelumab highly uncertain (see paragraph 6.60). The PBAC noted with the price proposed for nivolumab in the July 2022 submission (AEMP of $| | per 100 mg vial) the ICER for the multivariate analysis decreased to $5,000 to < $15,000 per QALY. The PBAC also noted the ICER using the effective price of avelumab and considered nivolumab would be cost-effective at the price proposed in the July 2022 submission.
	8. The PBAC noted the net financial impact to the PBS/RPBS increased relative to the July 2022 submission, despite narrowing of the patient population eligible for treatment and including cost-offsets of avelumab maintenance use. This was due to an increase in the proportion of patients who uptake NAC due to the listing of nivolumab (from 44.2% in the absence of nivolumab listing to 67.4% by Year 6), the high rate of uptake of nivolumab assumed (90%) and a higher nivolumab price. The PBAC acknowledged the assumptions around the proportion of patients who uptake NAC due to the listing of nivolumab were uncertain but considered them likely reasonable. The PBAC also considered that an uptake rate of 90% was appropriate now that the proposed PBS population was restricted to patients who had received prior NAC. The PBAC noted the Pre-Sub-Committee Response (PSCR) provided revised financial estimates based on AIHW incidence projections for bladder cancer, a 10 month stopping rule for avelumab and an assumption that, in the absence of nivolumab, 43% of patients would otherwise have developed a distant recurrence and used avelumab. However, the PSCR financial estimates did not include AIHW estimates for other urinary organs or address the error identified by the evaluation regarding how distant recurrences have been estimated in Years 2 onwards (see paragraph 6.87). The PBAC considered these omissions from the PSCR financial estimates should be corrected with revised estimates also updated with the results of the pricing negotiations outlined in paragraph 7.7.
	9. The PBAC considered that a Risk Sharing Arrangement would be required to manage the uncertainty associated with the proportion of patients who uptake NAC due to the listing of nivolumab and to manage the risk of use outside of the proposed PBS population.

**Outcome:**

Deferred

1. 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.

1. Sponsor’s Comment

Bristol-Myers Squibb Australia looks forward to continuing to work with the PBAC and the Department of Health and Aged Care to provide timely access to nivolumab for the adjuvant treatment of high-risk muscle invasive urothelial carcinoma.

1. AusPAR - OPDIVO - Nivolumab - Bristol-Myers Squibb Australia Pty Ltd - PM-2021-02518-1-4 Final 6 June 2023 [↑](#footnote-ref-2)
2. In urothelial carcinoma, the following coding is used to describe regional lymph node involvement: N+ denotes node positivity. NX: The regional lymph nodes cannot be evaluated. N0: The cancer has not spread to the regional lymph nodes. N1: The cancer has spread to 1 regional lymph node in the pelvis. N2: The cancer has spread to 2 or more regional lymph nodes in the pelvis. N3: The cancer has spread to the common iliac lymph nodes, which are located behind the major arteries in the pelvis, above the bladder. [↑](#footnote-ref-3)
3. ypT2 denotes preoperative radiotherapy or chemotherapy (y) in a primary (p) tumour of T2 stage (or primary tumour invading muscularis propria).

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

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

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

pT3, pT4a and pN+ denote the same as above, but without preoperative radiotherapy or chemotherapy (y). [↑](#footnote-ref-4)
4. Rouprêt M et al. EAU guidelines on upper urinary tract urothelial carcinoma. Disease management [Internet] Arnhem, The Netherlands. European Association of Urology. 2019. [↑](#footnote-ref-5)
5. Round 2 TGA CER for nivolumab, Submission PM-2021-02518-1-4, p22. [↑](#footnote-ref-6)
6. European Association of Urology (https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma/chapter/disease-management) [↑](#footnote-ref-7)
7. 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 [↑](#footnote-ref-8)
8. European Association of Urology (https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer/chapter/disease-management) [↑](#footnote-ref-9)
9. Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017 [↑](#footnote-ref-10)
10. The condition must have progressed on or after prior platinum-based chemotherapy; OR The condition must have progressed on or within 12 months of completion of adjuvant platinum-containing chemotherapy following cystectomy for localised muscle-invasive urothelial cancer; OR The condition must have progressed on or within 12 months of completion of neoadjuvant platinum-containing chemotherapy prior to cystectomy for localised muscle-invasive urothelial cancer. [↑](#footnote-ref-11)
11. Sourced from Galsky MD et al. Extended follow-up results from the CheckMate 274 trial. ASCO Genitourinary Cancers Symposium 2023. Abstract LBA443. [↑](#footnote-ref-12)
12. European Organisation for Research and Treatment of Care Quality of Life Questionnaire [↑](#footnote-ref-13)
13. 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;22(4):525-37 [↑](#footnote-ref-14)
14. Bellmunt J et al. Randomized Phase III Study Comparing Paclitaxel/Cisplatin/ Gemcitabine and Gemcitabine/Cisplatin in Patients With Locally Advanced or Metastatic Urothelial Cancer Without Prior Systemic Therapy: EORTC Intergroup Study 30987. *Journal of Clinical Oncology*. 2012;30(10):1107-13. [↑](#footnote-ref-15)
15. DeSantis M et al. Randomized Phase II/III Trial Assessing Gemcitabine/Carboplatin and Methotrexate/Carboplatin/Vinblastine in Patients With Advanced Urothelial Cancer Who Are Unfit for Cisplatin-Based Chemotherapy: EORTC Study 30986*. Journal of Clinical Oncology*. 2012;30(2):191-9. [↑](#footnote-ref-16)
16. Powles T et al. Avelumab first-line maintenance for advanced urothelial carcinoma: results from the JAVELIN Bladder 100 trial after≥ 2 years of follow-up. *Journal of Clinical Oncology*. 2023;41(19):3486. [↑](#footnote-ref-17)
17. Viney R et al. Time trade-off derived EQ-5D weights for Australia. *Value Health*. 2011 Sep-Oct;14(6):928-36. [↑](#footnote-ref-18)
18. Kong J 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 [↑](#footnote-ref-19)
19. Zhai M et al. Short-term mortality risks among patients with non-metastatic bladder cancer. *BMC Cancer*. 2020 2020/11/25;20(1):1148 [↑](#footnote-ref-20)
20. Bregman B, Teitsson S, Orsini I, Cotté F-E, Amadi A, Moshyk A, et al. Cost–Utility Analysis of Nivolumab in Adjuvant Treatment of Melanoma in France. *Dermatology and Therapy*. 2020 2020/12/01;10(6):1331-43. [↑](#footnote-ref-21)
21. Australian Institute of Health Welfare. Cancer in Australia 2021. Canberra: AIHW 2021. Report No.: Cancer series no. 133. Cat. no. CAN 144. [↑](#footnote-ref-22)