

**6.02 AVELUMAB,
Solution concentrate for I.V. infusion 200 mg in
10 mL,
Bavencio[®],
Merck Healthcare Pty Ltd.**

1 Purpose of submission

- 1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy), Authority Required (Streamlined) listing of avelumab, for the maintenance treatment of locally advanced (Stage III) or metastatic (Stage IV) urothelial carcinoma in patients whose disease has not progressed following first-line platinum-based chemotherapy. Listing for avelumab was requested on the basis of a cost-effectiveness analysis of avelumab + best supportive care (BSC) versus BSC. The PBAC has not previously considered avelumab for this indication.

Table 1: Key components of the clinical issue addressed in the submission

| Component | Description |
|----------------|--|
| Population | Patients with unresectable locally advanced (Stage III) or metastatic (Stage IV) urothelial carcinoma whose disease has not progressed with first-line platinum-based chemotherapy. |
| Intervention | Avelumab 800 mg by intravenous infusion every 2 weeks |
| Comparator | Best supportive care, representing watch and wait monitoring ¹ |
| Outcomes | Overall survival, progression-free survival, safety, quality of life. |
| Clinical claim | In patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed on first-line platinum-based chemotherapy, avelumab is superior in terms of overall and progression-free survival, and inferior in terms of safety compared to best supportive care. |

Source: Table 1.1-1, p15 of the submission.

¹ Best supportive care in JAVELIN Bladder 100 trial included treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management (including palliative radiotherapy), but did not include any active antitumour therapy.

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** The submission was submitted under the TGA/PBAC parallel process. Avelumab was registered on 24 February 2021 for the first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma, whose disease has not progressed with first-line platinum-based induction chemotherapy.
- 2.2 Avelumab was registered on the ARTG in January 2018 for the treatment of adults and paediatric patients 12 years and older with metastatic Merkel cell carcinoma. Avelumab was registered on the ARTG in May 2020 for use in combination with axitinib for the first-line treatment of patients with advanced renal cell carcinoma.

Public Summary Document– March 2021 PBAC Meeting

3 Requested listing

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

| Name, Restriction, Manner of administration and form | PBS item code | Max. Amount | No. of Rpts | Dispensed price for maximum amount | Manufacturer |
|---|-------------------------------|-------------|-------------|---|--------------------------|
| AVELUMAB, 200 mg/10 mL injection, 10 mL vial | NEW (Public) NEW (Private) | 800 | 7 | Public: \$5,515.22 (published) \$ [REDACTED] (effective) Private: \$5,631.86 (published) \$ [REDACTED] (effective) | Merck Healthcare Pty Ltd |
| Available brands | | | | | |
| Bavencio (avelumab 200 mg/10 mL injection, 10 mL vial) | | | | | |

Initial treatment Restriction Summary [NEW] / Treatment of Concept (ToC): [NEW]

| | |
|-------------------------------|---|
| Category / Program: | Section 100 – Efficient Funding of Chemotherapy |
| Prescriber type: | Medical Practitioners |
| Severity: | Locally advanced (Stage III) or metastatic (Stage IV) |
| Condition: | Urothelial cancer |
| PBS Indication: | Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer [21171] |
| Treatment phase: | <i>Maintenance therapy - Initial treatment</i> |
| Restriction Level: | <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (Telephone/electronic) <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | |
| | Patient must have received at least one previous first-line platinum-based chemotherapy containing regimens, |
| | AND |
| Clinical criteria: | |
| | Patient must not have progressive disease following <i>first-line</i> platinum-based chemotherapy |
| | AND |
| Clinical criteria: | |
| | <i>Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition</i> |
| | AND |
| Clinical criteria: | |
| | Patient must have a WHO performance status of 0 or 1, |
| | AND |
| Clinical criteria: | |
| | The treatment must be the sole PBS-subsidised therapy for this condition |
| Administrative advice: | |
| | <i>In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.</i> |
| Administrative advice: | |
| | <i>No increase in the maximum quantity or number of units may be authorised.</i> |
| Administrative advice: | |
| | <i>No increase in the maximum number of repeats may be authorised.</i> |
| Administrative advice: | |
| | <i>Special Pricing Arrangements apply</i> |

Public Summary Document– March 2021 PBAC Meeting

Grandfathering treatment Restriction Summary [NEW] / Treatment of Concept (ToC): [NEW]

| | |
|-------------------------------|---|
| Category / Program: | Section 100 – Efficient Funding of Chemotherapy |
| Prescriber type: | Medical Practitioners |
| Severity: | Locally advanced (Stage III) or metastatic (Stage IV) |
| Condition: | Urothelial cancer |
| PBS Indication: | Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer |
| Treatment phase: | <i>Maintenance therapy – Grandfathering treatment</i> |
| Restriction Level: | <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (Telephone/electronic) (<input checked="" type="checkbox"/> Streamlined) |
| Clinical criteria: | |
| | Patient must have received non-PBS-subsidised treatment with this drug for this indication prior to [date of PBS listing], |
| | AND |
| Clinical criteria: | |
| | Patient must have received <i>first-line</i> platinum-based chemotherapy prior to initiation of non-PBS-subsidised treatment with this drug for this condition, |
| | AND |
| Clinical criteria: | |
| | Patient must not have progressive disease following <i>first-line</i> platinum-based chemotherapy |
| | AND |
| Clinical criteria: | |
| | Patient must have had a WHO performance status of 0 or 1 prior to initiation of non-PBS-subsidised treatment with this drug for this condition, |
| | AND |
| Clinical criteria: | |
| | Patient must not have developed disease progression while being treated with this drug for this condition, |
| | AND |
| Clinical criteria: | |
| | The treatment must be the sole PBS-subsidised therapy for this condition |
| | AND |
| Clinical criteria: | |
| | <i>Patient must not have received prior treatment with a PBS-subsidised programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition</i> |
| Administrative advice: | |
| | <i>In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.</i> |
| Administrative advice: | |
| | <i>No increase in the maximum quantity or number of units may be authorised.</i> |
| Administrative advice: | |
| | <i>No increase in the maximum number of repeats may be authorised.</i> |
| Administrative advice: | |
| | <i>Special Pricing Arrangements apply</i> |

Public Summary Document– March 2021 PBAC Meeting

| Name, Restriction, Manner of administration and form | PBS item code | Max. Amount | No. of Rpts | Dispensed price for maximum amount | Manufacturer |
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| Available brands | | | | | |
| Bavencio (avelumab 200 mg/10 mL injection, 10 mL vial) | | | | | |

Continuing treatment Restriction Summary [NEW] / Treatment of Concept (ToC): [NEW]

| | |
|-------------------------------|--|
| Category / Program: | Section 100 – Efficient Funding of Chemotherapy |
| Prescriber type: | Medical Practitioners |
| Severity: | Locally advanced (Stage III) or metastatic (Stage IV) |
| Condition: | Urothelial cancer |
| PBS Indication: | Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer [21171] |
| Treatment phase: | <i>Maintenance therapy – Continuing treatment</i> |
| Restriction Level: | <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (Telephone/electronic) <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | |
| | Patient must have previously received PBS-subsidised treatment with this drug for this condition, |
| | AND |
| Clinical criteria: | |
| | Patient must have stable or responding disease Patient must not have developed disease progression while being treated with this drug for this condition |
| | AND |
| Clinical criteria: | |
| | The treatment must be the sole PBS-subsidised therapy for this condition, |
| | AND |
| Clinical criteria: | |
| | The treatment must be maintenance therapy. |
| | AND |
| Administrative advice: | No increase in the maximum quantity or number of units may be authorised. |
| Administrative advice: | No increase in the maximum number of repeats may be authorised. |
| Administrative advice: | Special Pricing Arrangements apply |

- 3.2 The submission requested a special pricing arrangement for avelumab with an effective Public hospital DPMA of \$ [REDACTED] (published DPMA: \$5,515.22).
- 3.3 The submission proposed a Streamlined authority listing for avelumab so that the restriction is consistent with the current PBS listing for pembrolizumab. The PBAC considered an Authority Required (Telephone/Electronic) listing may be more appropriate for avelumab to allow WHO performance status and prior platinum-based chemotherapy status to be checked by Services Australia.
- 3.4 The proposed restriction is narrower than the proposed TGA indication, which does not limit treatment on the basis of WHO performance status or on the basis of disease stage; as well as the pembrolizumab listing which requires a performance status of 2

or less. The PBAC considered including the WHO performance status for avelumab was appropriate and noted that a performance score of 0 or 1 was consistent with the inclusion criteria of the JAVELIN Bladder 100 trial.

- 3.5 Eligibility criteria for the JAVELIN Bladder 100 trial required documented Stage IV disease, which differs from the population specified in the requested restriction which included Stage III and Stage IV disease. The ESC noted that the inclusion of Stage III and Stage IV was consistent with the current pembrolizumab restriction. While the financial estimates presented in the submission include patients with Stage III and Stage IV disease, the economic analysis presented was based on the results of the JAVELIN Bladder 100 trial, and may not reflect the population in which the listing is sought. Additionally, the JAVELIN Bladder 100 trial recruited patients with unresectable disease, which is not required under the proposed restriction. The ESC noted that according to the AJCC Staging Manual patients can have Stage IV disease without metastases which could be considered 'locally advanced' (e.g. T4 N0 M0, see paragraph 4.4). The DUSC and ESC agreed with the evaluation that the inclusion of reference to Stage III disease in the proposed PBS indication meant that the PBS population would be broader than the trial population. The PBAC considered that both Stage III and Stage IV disease should be included in the PBS listing to be consistent with the current listing for pembrolizumab.
- 3.6 Under the proposed restriction, patients must not have experienced disease progression following platinum-based chemotherapy. The proposed restriction does not specify a required number of platinum-containing chemotherapy cycles. In the JAVELIN Bladder 100 trial, patients were required to have completed 4 to 6 cycles of chemotherapy with gemcitabine + cisplatin and/or gemcitabine + carboplatin. The proposed restriction does not specify the timing of platinum-containing chemotherapy in relation to the commencement of treatment with avelumab. In the JAVELIN Bladder 100 trial, patients were required to have received the last dose of chemotherapy no less than 4 weeks and no more than 10 weeks prior to randomisation. The TGA CER (p13) noted that while the Australian eviQ guidelines recommend treatment with a platinum-based regimen until disease progression or unacceptable toxicity, treatment is usually for 6 cycles. The Pre-Sub-Committee Response (PSCR) noted that 4 to 6 cycles would be standard practice in Australia based on advice from the sponsor's urothelial cancer advisory board meeting. The ESC considered 4 to 6 cycles appropriate, however DUSC noted that in practice, patients may not reach four cycles of treatment due to the toxic nature of platinum therapy, urothelial carcinoma being burdensome and the significant number of comorbidities in these patients. The PBAC considered the number of platinum-containing chemotherapy cycles administered would likely be based on clinical judgement.
- 3.7 The proposed restriction does not include any requirements regarding PD-L1 expression status. While an improvement in overall survival was reported among the subgroup of patients with PD-L1 negative tumours at baseline in the JAVELIN Bladder 100 trial, the difference between avelumab + BSC and BSC was not statistically

significant. The ESC considered the benefit in the PD-L1 negative subgroup was unclear based on the clinical data (see paragraph 6.30).

- 3.8 The proposed restriction does not preclude repeat courses of avelumab among patients who receive retreatment with platinum-based chemotherapy. To reduce the potential for use of avelumab in a latter line setting the DUSC and ESC considered that the initial treatment criteria referencing platinum-based chemotherapy should be modified to include reference to its use in the first-line setting.
- 3.9 There is potential for use outside of the proposed restriction among patients with disease progression following platinum-based chemotherapy, or among patients who continue treatment despite experiencing disease progression. No maximum duration of treatment was proposed in the requested restrictions. As such, the PBAC considered it appropriate for the following clinical criterion to be included in the continuing restriction ‘Patient must not have developed disease progression’ and advised that this change should flow on to the listing for pembrolizumab. In addition, for consistency with the pembrolizumab restriction, the PBAC considered the following administrative advice should be included in the initial treatment restriction ‘In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.’
- 3.10 The submission stated that it is anticipated that the proposed listing of avelumab in the first-line maintenance setting will necessitate flow-on restriction changes to the pembrolizumab listing to prevent sequential use of PD-L1/PD-1 inhibitors. The ESC noted that the JAVELIN Bladder 100 trial excluded patients with prior immunotherapy with PD-L1/PD-1 inhibitors. The ESC considered that including reference to the first-line setting in the clinical criteria of the proposed restriction (see paragraph 3.8) would allow consistency with the prior PD-L1/PD-1 inhibitor status of trial participants. The PBAC considered that the following clinical criterion should be flowed on to the current listing for pembrolizumab “Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition”.
- 3.11 The PBAC considered that it was appropriate to have a grandfather restriction to allow continued treatment for patients who access non-PBS subsidised avelumab prior to listing.

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

4 Population and disease

- 4.1 Urothelial carcinomas are cancers that arise from urothelial cells of the transitional epithelium which lines the renal pelvis, ureters, urinary bladder, and urethra. The majority of urothelial carcinomas (>90%) originate in the bladder, around 8% originate in the renal pelvis, and the remainder occur in the ureter and urethra.
- 4.2 The incidence of bladder cancer is around 4 times higher in males than females. The Australian age-standardised incidence rate was 16.9 cases per 100,000 for males and 4.2 cases per 100,000 for females in 2019. Bladder cancer is associated with advancing age, with over 90% of new diagnoses occurring in individuals aged over 55 years. Patients with advanced or metastatic disease have a poor prognosis with a median survival of approximately 14 months (Bellmunt et al., 2014).
- 4.3 The submission defined locally advanced disease as being cancer which has grown through the bladder wall and into the pelvic or abdominal wall and/or spread to regional lymph nodes (TNM Stages T3 N0 M0, T4 N0 M0, or Tany N1-3 M0), and metastatic disease as being cancer that has spread to distant lymph nodes and/or spread to other organs outside of the bladder (Tany Nany M1). The submission stated that locally advanced or metastatic urothelial cancer is classified as Stage III or Stage IV, respectively, based on the American Joint Committee on Cancer (AJCC) staging system.
- 4.4 The ESC noted that AJCC staging for urothelial carcinoma differs based on the primary tumour site (urinary bladder, renal pelvis/ureter or urethra). Based on the current AJCC Staging Manual (8th edition, 2017), Stage III and IV prognostic groups are defined as follows:
- Urothelial carcinoma of the urinary bladder:
 - Stage III: T3 N0 M0, T4a N0 M0 or T1-4a N1-3 M0;
 - Stage IV: T4b Nany M0 or Tany Nany M1.
 - Urothelial carcinoma of the renal pelvis or ureter:
 - Stage III: T3 N0 M0;
 - Stage IV: T4 N0 M0, Tany N1-2 M0 or Tany Nany M1.
 - Urothelial carcinoma of the urethra:
 - Stage III: T1-3 N1 M0 or T3 N0 M0;
 - Stage IV: T4 N0-1 M0, Tany N2 M0 or Tany Nany M1.
- 4.5 The submission positioned avelumab as an alternative to watchful waiting for patients who have not experienced disease progression following treatment with platinum-containing chemotherapy. The NCCN Bladder Cancer Guidelines (Version 6.2020, July 2020) and the ESMO Bladder Cancer Clinical Practice Guidelines (Bellmunt et al., 2014; eUpdates December 2019 and July 2020) support the use of avelumab as first-line maintenance therapy for patients with locally advanced or metastatic disease (Stage IV) who have not experienced disease progression following platinum-containing chemotherapy.

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

5 Comparator

- 5.1 The submission nominated BSC, representing ‘watch and wait’ monitoring, as the main comparator. The main arguments provided in support of this nomination were:
- There is currently no maintenance treatment listed on the PBS for locally advanced or metastatic urothelial carcinoma following first-line treatment with platinum-based chemotherapy.
 - There have been no recent PBAC considerations of first-line maintenance treatment for locally advanced or metastatic urothelial carcinoma.
- 5.2 Best supportive care is an appropriate comparator. However, the use of avelumab in the first-line maintenance setting will result in downstream consequences to other PBS-listed medicines, including pembrolizumab, which is PBS-listed for the treatment of urothelial carcinoma in patients who have experienced disease progression following treatment with platinum-based chemotherapy.
- 5.3 The ESC considered that an appropriate comparator may be BSC, which represented watch and wait monitoring, and subsequent therapy with pembrolizumab as this would be reflective of what avelumab would replace in clinical practice. The PBAC agreed with ESC that BSC + subsequent therapy with pembrolizumab was an appropriate comparator.
- 5.4 A number of PD-L1/PD-1 inhibitors are currently being trialled in the first-line treatment setting, either in combination with platinum-based chemotherapy or as first-line maintenance therapy following treatment with platinum-based chemotherapy, but interim results have been mixed. The PBAC previously noted there was emerging data suggesting decreased survival when PD-1 inhibitors are used as first-line monotherapy in PD-L1-low expressing urothelial cancer (paragraph 2.3, pembrolizumab Public Summary Document (PSD), July 2018 PBAC meeting).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented a clinical statement which discussed the evidence for PD-L1 staining in predicting outcomes for immunotherapy in urothelial cancer. The clinician stated that evidence for PD-L1 staining in predicting outcome for immunotherapy in urothelial cancer is poor. The clinician noted the JAVELIN Bladder 100 trial was not powered to show a statistical response in the PD-L1 negative subgroup analysis, however, like the KEYNOTE-045 study of pembrolizumab, a numerical advantage was seen in PD-L1 negative patients but the difference was not statistically significant. The clinician also addressed

concerns regarding the treatment duration (see paragraph 6.67), stating that it would be expected to be long in the enriched population of chemotherapy-sensitive (and probably immune-sensitive) patients enrolled in the JAVELIN Bladder 100 trial.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from BEAT Bladder Cancer Australia and Rare Cancers Australia highlighted the negative impact on quality of life associated with this condition as a result of symptoms such as pain, weight loss and frailty. The comments also described the benefits associated with avelumab treatment such as providing an active approach to ongoing treatment and potentially extending survival.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the avelumab submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the JAVELIN Bladder 100 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for avelumab, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on a comparison with BSC alone.

Clinical trials

- 6.4 The submission was based on one head-to-head randomised trial comparing avelumab + BSC to BSC alone (JAVELIN Bladder 100).
- 6.5 Details of the JAVELIN Bladder 100 trial are presented in the table below.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Public Summary Document– March 2021 PBAC Meeting

Table 2: Trials and associated reports presented in the submission

| Trial ID | Protocol title/Publication title | Publication citation |
|-----------------------------------|--|---|
| JAVELIN Bladder 100 (NCT02603432) | <p>A Phase 3, Multicenter, Multinational, Randomized, Open-Label, Parallel-Arm Study of Avelumab (MSB0010718C) Plus Best Supportive Care Versus Best Supportive Care Alone as a Maintenance Treatment in Patients With Locally Advanced or Metastatic Urothelial Cancer Whose Disease Did Not Progress After Completion of First-Line Platinum-Containing Chemotherapy.</p> <p>A Phase 3, multicenter, multinational, randomized, open-label, parallel arm study of avelumab (MSB0010718C) plus best supportive care versus best supportive care alone as a maintenance treatment in patients with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum-containing chemotherapy.</p> <p>Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial cancer.</p> <p>Powles T, Park SH, Voog E, et al. Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line (1L) chemotherapy in advanced urothelial carcinoma (UC): JAVELIN Bladder 100 Phase III interim analysis.</p> | <p>Clinical study report, 24 February 2020.</p> <p>Study protocol, 28 March 2019.</p> <p><i>New England Journal of Medicine</i> 2020; 383(13):1218-30.</p> <p><i>Journal of Clinical Oncology</i> 2020; 38, no. 18_suppl.</p> |

Selected citations relating to conference abstracts omitted.

Source: Table 2.2-1, p.44 of the submission.

6.6 The key features of the JAVELIN Bladder 100 trial are summarised in the table below.

Table 3: Key features of the included evidence

| Trial | N | Design/duration | Risk of bias | Patient population | Outcomes | Use in modelled evaluation |
|-------------------------------|-----|--|--------------|--|--|---------------------------------|
| Avelumab + BSC vs. BSC | | | | | | |
| JAVLELIN Bladder 100 | 700 | Randomised, multi-centre (international) open-label, parallel-arm trial (median follow-up 19 months) | Unclear | <ul style="list-style-type: none"> - Unresectable locally advanced or metastatic urothelial carcinoma (documented Stage IV disease) - Prior first-line chemotherapy (4-6 cycles of gemcitabine + cisplatin and/or gemcitabine + carboplatin), with last dose received between 4 and 10 weeks prior - Absence of progressive disease per RECIST v1.1 following completion of first-line chemotherapy - ECOG of 0 or 1 | OS, PFS, ORR, safety, QoL (EQ-5D-5L, FACT FBISL) | OS, PFS, safety, QoL (EQ-5D-5L) |

Source: Table 2.4-1, p55; Table 2.4-4, p60 of the submission; Section 9.3, pp24-25 of the JAVELIN Bladder 100 clinical study report, Attachment 1A of the submission.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQoL 5-Dimension; FACT FBISL, Functional Assessment of Cancer Therapy Bladder Cancer Symptom Index-18; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours.

6.7 The JAVELIN Bladder 100 trial recruited patients with Stage IV, unresectable locally advanced or metastatic transitional cell carcinoma of the urothelium. Disease stage was based on the 7th edition of the AJCC Cancer Staging Manual, and included T4b N0 M0, Tany N1-3 M0, and Tany Nany M1 for urothelial carcinoma of the bladder; T4 N0 M0, Tany N1-3 M0 or Tany Nany M1 for urothelial carcinoma of the renal pelvis or ureter; and T4 N0-1 M0, Tany N1-2 M0 and Tany Nany M1 for urothelial carcinoma of the urethra.

- 6.8 The JAVELIN Bladder 100 trial had an unclear risk of bias. As the trial was open label, investigators, patients, and study personnel were not blinded to treatment allocation, which may have influenced the treatment of patients in the trial. Assessments made by study investigators (who were not blinded to treatment allocation) were at high risk of bias. The trial also included assessments by a blinded independent review committee, which had a lower risk of assessment bias. The trial was stopped at the interim analysis as the efficacy boundaries for overall survival had been crossed in the overall population and the PD-L1 positive population. The interim analysis became the final analysis for the study and is used as the basis for the current submission.
- 6.9 The clinical study report stated that if radiologic imaging showed progressive disease as per independent review committee assessment, patients treated with avelumab + BSC might have continued to receive avelumab at the investigator’s discretion and after discussion with the sponsor, if certain criteria were met.
- 6.10 Best supportive care included treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy) but could not include any active anti-tumour therapy. However, the use of subsequent anticancer treatments was permitted following independent review committee confirmation of disease progression. Cross-over to receive avelumab following disease progression was not permitted.
- 6.11 Table 4 presents a summary of subsequent anticancer treatments reported for the avelumab + BSC and BSC arms in the JAVELIN Bladder 100 trial.

Table 4: Subsequent anticancer treatments in the JAVELIN Bladder 100 trial

| | AVE + BSC (N=350) | BSC (N=350) |
|---|------------------------------|------------------------|
| Discontinued randomised study treatment, n (%) | 265 (75.7) | 324 (92.6) |
| At least one follow-up anticancer therapy, n (%) | | |
| - Yes | 148 (42.3) | 216 (61.7) |
| - No | 73 (20.9) | 50 (14.3) |
| - Unknown | 129 (36.9) | 84 (24.0) |
| Number of follow-up anti-cancer drug therapy regimens | | |
| - 0 regimens | 73 (20.9) | 50 (14.3) |
| - 1 regimens | 102 (29.1) | 150 (42.9) |
| - 2 regimens | 33 (9.4) | 52 (14.9) |
| - 3 regimens | 11 (3.1) | 11 (3.1) |
| - ≥4 regimens | 2 (0.6) | 3 (0.9) |
| - Not reported | 129 (36.9) | 84 (24.0) |
| Any PD-1 or PD-L1 inhibitor, n (%) | 22 (6.3) | 153 (43.7) |
| FGFR inhibitor, n (%) | 9 (2.6) | 8 (2.3) |
| Any other drug therapy, n (%) | 140 (40.0) | 119 (34.0) |
| Drug therapy ≥2% in either treatment arm, n (%) | | |
| - Gemcitabine | 61 (17.4) | 52 (14.9) |
| - Paclitaxel | 48 (13.7) | 41 (11.7) |
| - Carboplatin | 46 (13.1) | 36 (10.3) |
| - Vinflunine | 37 (10.6) | 17 (4.9) |
| - Cisplatin | 29 (8.3) | 21 (6.0) |
| - Pembrolizumab | 19 (5.4) | 71 (20.3) |
| - Pemigatinib | 7 (2.0) | 3 (0.9) |
| - Docetaxel | 5 (1.4) | 10 (2.9) |
| - Atezolizumab | 3 (0.9) | 49 (14.0) |
| - Nivolumab | 0 | 18 (5.1) |
| - Durvalumab | 0 | 16 (4.6) |

Source: Table 2.5-3, p71 of the submission; Table 14.4.2.7.1, p651-652; Table 14.4.2.7.1.3, pp660-662 of clinical study report, Appendix 1B of the submission.

Abbreviations: AVE, avelumab; BSC, best supportive care; FGFR, fibroblast growth factor receptor; PD-1, programmed death protein; PD-L1, programmed death-ligand 1.

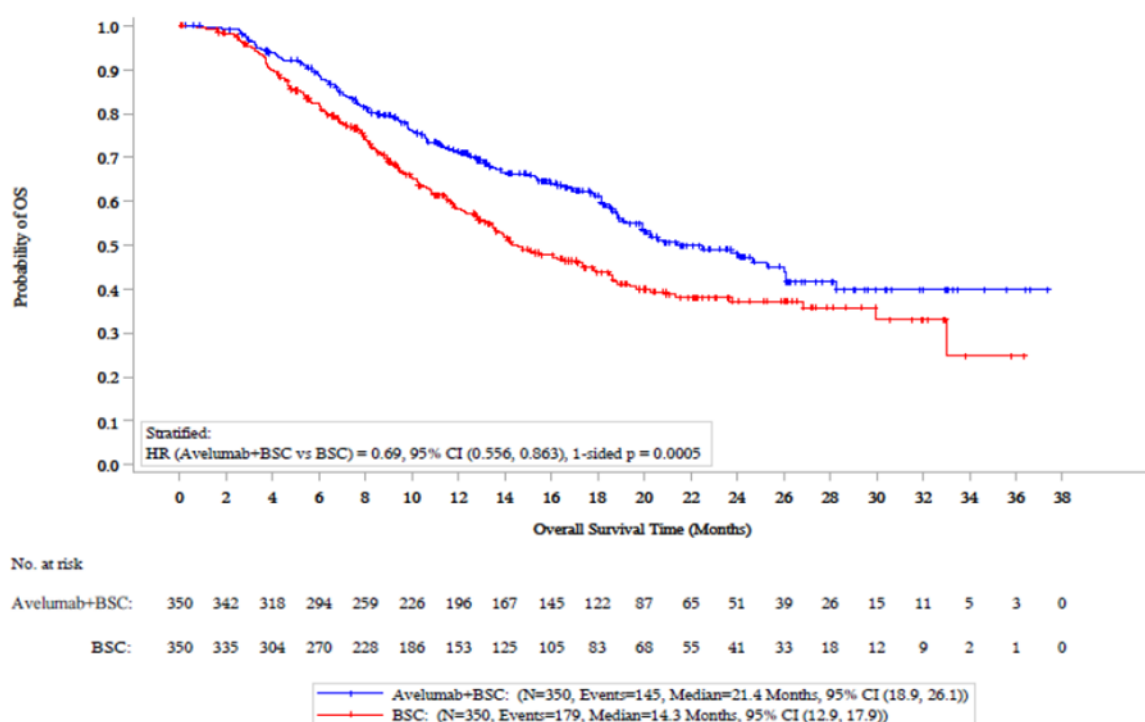
- 6.12 At least one subsequent anticancer therapy was reported in 42.3% of patients in the avelumab + BSC arm and 61.7% in the BSC arm at the time of the interim analysis. The use of subsequent anticancer treatment was reported as unknown for 36.9% of patients in the avelumab + BSC arm and 24.0% of patients in the BSC arm.
- 6.13 In the BSC arm, 43.7% (153/350) of patients received subsequent treatment with a PD-1/PD-L1 inhibitor. This equates to 70.8% (153/216) as a proportion of the patients who received a subsequent anti-cancer therapy or 61% (153/251) of patients who experienced disease progression in the BSC arm. In the avelumab + BSC arm, 6.3% (22/350) of patients received subsequent treatment with a PD-1/PD-L1 inhibitor. The PSCR acknowledged that in Australian clinical practice a greater proportion of patients (80%) treated with BSC alone receive second-line treatment with a PD-1/PD-L1 inhibitor than that observed in the JAVELIN Bladder 100 trial. However, the PSCR argued that given the severity of locally advanced or metastatic urothelial carcinoma and the average age of this patient population, it was reasonable to consider that a proportion of patients who experience disease progression following avelumab + BSC or BSC alone may not be fit enough to receive subsequent anti-cancer treatment. The

ESC considered the BSC arm of the trial was not reflective of standard care of in Australia and that the reported proportion of patients to receive second-line treatment with a PD-1/PD-L1 inhibitor (80%) was underestimated. The PBAC agreed with the pre-PBAC response that approximately 20% of patients with progressive disease may not be eligible for subsequent treatment with a PD-1/PD-L1 inhibitor.

Comparative effectiveness

6.14 Figure 1 presents the Kaplan-Meier plot of overall survival for the JAVELIN Bladder 100 trial (median follow-up 19.6 months for the avelumab + BSC arm, 19.2 months for the BSC arm).

Figure 1: Kaplan-Meier plot of overall survival for the JAVELIN Bladder 100 trial



Source: Figure 2.5-4, p68 of the submission.

Abbreviations: BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival.

6.15 Table 5 presents the overall survival results for the JAVELIN Bladder 100 trial.

Table 5: Overall survival results for the JAVELIN Bladder 100 trial

| Cohort | AVE + BSC (N=350) | BSC (N=350) |
|--|----------------------|----------------------|
| Median duration of follow-up, months (range) | 19.6 (18.0 - 20.6) | 19.2 (17.4 - 21.6) |
| Subjects with event, n (%) | 145 (41.4) | 179 (51.1) |
| Median OS, months (95% CI) | 21.4 (18.9, 26.1) | 14.3 (12.9, 17.9) |
| Stratified HR (95% CI) | 0.69 (0.556, 0.863) | |
| KM estimate of OS | | |
| - 6 months, % (95% CI) | 0.888 (0.849, 0.917) | 0.822 (0.777, 0.859) |
| - 12 months, % (95% CI) | 0.713 (0.660, 0.760) | 0.584 (0.527, 0.637) |
| - 18 months, % (95% CI) | 0.613 (0.554, 0.667) | 0.438 (0.378, 0.497) |
| - 24 months, % (95% CI) | 0.481 (0.413, 0.547) | 0.372 (0.309, 0.434) |
| - 30 months, % (95% CI) | 0.398 (0.318, 0.477) | 0.330 (0.252, 0.411) |

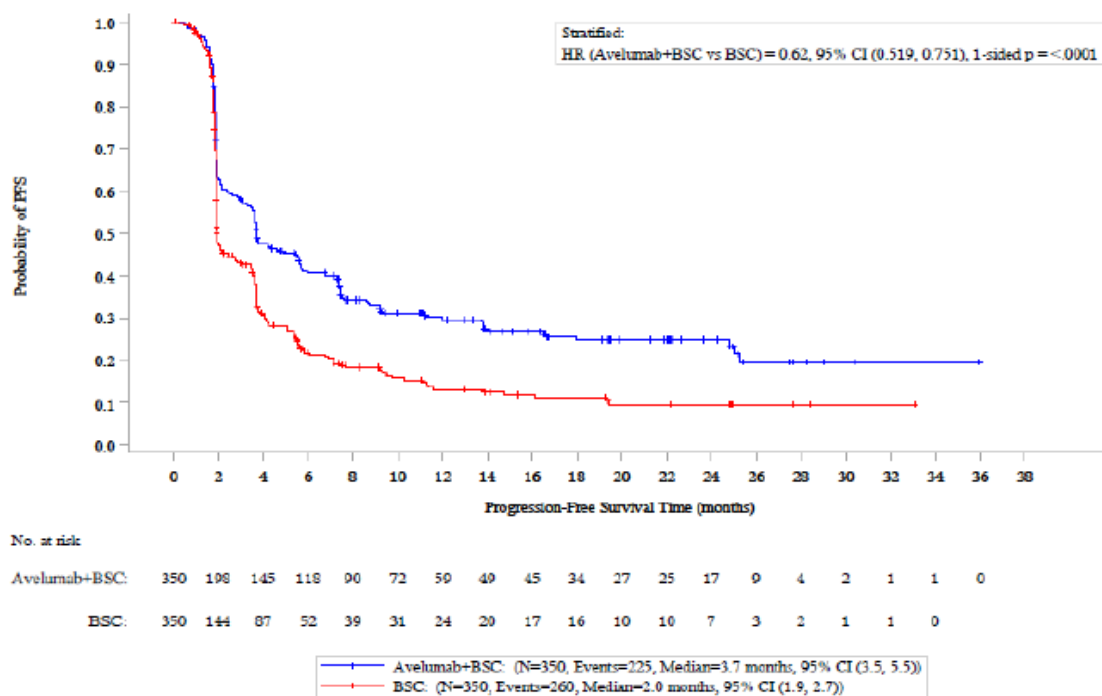
Source: Table 13, pp62-63 of the JAVELIN Bladder 100 clinical study report, Appendix 1A of the submission.

Abbreviations: AVE, avelumab; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival.

- 6.16 At a median duration of follow-up of 19.6 months for avelumab + BSC and 19.2 months for BSC, overall survival was statistically significantly longer in the avelumab + BSC arm compared to the BSC arm (median overall survival 21.4 months for avelumab + BSC versus 14.3 months for BSC; hazard ratio = 0.69 [95% CI: 0.56, 0.86]). The ESC considered overall survival in the BSC arm of the JAVELIN Bladder 100 trial was likely underestimated due to a lower proportion of patients receiving subsequent treatment with a PD-1/PD-L1 inhibitor than would be expected in the Australian setting (see paragraph 6.13). As such, the ESC considered the overall survival results were uncertain and favoured avelumab.
- 6.17 The pre-PBAC response noted that in the BSC arm, 120/216 (55.5%) of patients who received subsequent therapy received immunotherapy as second-line treatment. The pre-PBAC response presented an ad-hoc analysis of overall survival for the following subgroups of the BSC arm of the JAVELIN Bladder 100 trial: subjects without subsequent anti-cancer drug therapies (n=134); subjects with subsequent second-line PD-1/PD-L1 inhibitor therapies (n=120); and subjects with subsequent second-line anti-cancer non PD-1/PD-L1 containing therapies (n=96). The median overall survival estimates for the subgroups were reported as 13.3 months (95% CI: 10.3, 26.8), 16.5 months (95% CI: 13.5, 30.0) and 14.0 months (95% CI: 11.4, 17.8) respectively. The pre-PBAC response argued that the median overall survival is very similar between patients that received second-line treatment with a PD-1/PD-L1 and those that received second-line treatment with medicines other than PD-1/PD-L1. The pre-PBAC response also argued that the median overall survival for the subgroup of patients in the BSC arm who received subsequent second-line PD-1/PD-L1 inhibitor therapies was consistent with the observed median overall survival for the BSC in the ITT population (14.3 months, 95%CI: 12.9, 17.9). The pre-PBAC response concluded that, based on this ad-hoc analysis, it is plausible to assume that the median overall survival estimate for any adjusted analysis would likely have minimal impact, given the adjusted overall survival would be between 14.0 and 16.5 months.

6.18 Figure 2 presents the Kaplan-Meier plot of independent review committee-assessed progression-free survival for the JAVELIN Bladder 100 trial (median follow-up 19.6 months for the avelumab + BSC arm and 19.2 months for the BSC arm).

Figure 2: Kaplan-Meier plot of independent review committee-assessed progression-free survival for the JAVELIN Bladder 100 trial



Source: Figure 2.5-1, p63 of the submission.

Abbreviations: BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

6.19 Table 6 summarises the results for independent review committee and investigator-assessed progression-free survival for the JAVELIN Bladder 100 trial.

Table 6: Progression-free survival results for the JAVELIN Bladder 100 trial

| Cohort | AVE + BSC (N=350) | BSC (N=350) |
|--|----------------------|----------------------|
| Median duration of follow-up, months (range) | 19.6 (18.0 - 20.6) | 19.2 (17.4 - 21.6) |
| Independent review committee-assessed | | |
| Subjects with event, n (%) | 225 (64.3) | 260 (74.3) |
| - Progression, n (%) | 216 (61.7) | 251 (71.7) |
| - Death, n (%) | 9 (2.6) | 9 (2.6) |
| Median PFS, months (95% CI) | 3.7 (3.5, 5.5) | 2.0 (1.9, 2.7) |
| Stratified HR (95% CI) | 0.62 (0.519, 0.751) | |
| KM estimate of PFS | | |
| - 3 months, % (95% CI) | 0.581 (0.525, 0.634) | 0.427 (0.371, 0.481) |
| - 6 months, % (95% CI) | 0.407 (0.352, 0.461) | 0.218 (0.172, 0.267) |
| - 9 months, % (95% CI) | 0.330 (0.278, 0.384) | 0.184 (0.140, 0.232) |
| - 12 months, % (95% CI) | 0.296 (0.244, 0.350) | 0.131 (0.092, 0.178) |
| - 15 months, % (95% CI) | 0.269 (0.218, 0.323) | 0.119 (0.081, 0.165) |
| Investigator-assessed | | |
| Subjects with event, n (%) | 235 (67.1) | 277 (79.1) |
| - Progression, n (%) | 225 (64.3) | 271 (77.4) |
| - Death, n (%) | 10 (2.9) | 6 (1.7) |
| Median PFS, months (95% CI) | 5.5 (4.2, 7.2) | 2.1 (1.9, 3.0) |
| Stratified HR (95% CI) | 0.52 (0.437, 0.625) | |
| KM estimate of PFS | | |
| - 3 months, % (95% CI) | 0.682 (0.629, 0.729) | 0.445 (0.390, 0.500) |
| - 6 months, % (95% CI) | 0.460 (0.406, 0.513) | 0.234 (0.188, 0.283) |
| - 9 months, % (95% CI) | 0.387 (0.334, 0.440) | 0.167 (0.127, 0.212) |
| - 12 months, % (95% CI) | 0.341 (0.288, 0.394) | 0.116 (0.081, 0.157) |
| - 15 months, % (95% CI) | 0.304 (0.252, 0.358) | 0.092 (0.061, 0.131) |

Source: Table 14.2.4.1, pp32-33; Table 14.2.4.2, pp34-35, Attachment 1C of the submission.

Abbreviations: AVE, avelumab; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

- 6.20 At a median duration of follow-up of 19.6 months for the avelumab + BSC arm and 19.2 months for the BSC arm, independent review committee-assessed progression-free survival was statistically significantly longer in the avelumab + BSC arm compared to the BSC arm (median progression-free survival 3.7 months for avelumab + BSC versus 2.0 months for BSC; hazard ratio = 0.62 [95% CI: 0.52, 0.75]).
- 6.21 Results based on investigator assessment were consistent with the independent review committee results, with slightly longer progression-free survival among patients in the avelumab + BSC arm (median progression-free survival 5.5 months for avelumab + BSC versus 2.1 months for BSC; hazard ratio = 0.52 [95% CI: 0.44, 0.63]).
- 6.22 As per the criteria specified in paragraph 6.9, 120 patients in the avelumab + BSC arm with confirmed disease progression by both blinded independent review committee and investigator-assessment continued to receive avelumab. The mean number of infusions following confirmed progression was 5.7 (median 3.0; range: 1.0 - 44.0).
- 6.23 The submission argued that the large number of patients continuing treatment beyond disease progression was due to study treatment being continued until radiological confirmation of progressive disease, which was required at least 4 weeks from the first evidence of progression. The submission also suggested that continued treatment with avelumab in this context may reflect pseudo-progression or when an

investigator feels that there has not been enough time for the effect of the treatment to become evident. However, it is unclear whether this accounted for all instances of treatment beyond disease progression. The overall impact of treatment beyond disease progression on effectiveness and safety outcomes is unclear. The ESC noted that the mean number of infusions post-progression (5.7) equated to approximately 11.4 weeks of treatment. The ESC considered this was not consistent with the submission’s argument that most continuing use would be due to patients waiting for the confirmatory scan of disease progression undertaken 4 weeks after suspected progression.

- 6.24 The PSCR provided a subgroup analysis of overall survival excluding patients in the avelumab + BSC arm who received avelumab post progression (see Table 7). The PSCR argued that the analysis demonstrated that the statistically significant improvement in median overall survival observed in the ITT population in the JAVELIN Bladder 100 trial was not due to the use of avelumab post-progression. The ESC considered that although the data presented in the PSCR suggested that the effectiveness was similar, it did not answer questions regarding the impact of such use on safety outcomes or financial estimates.

Table 7: Overall survival results - subjects that continued avelumab after progression by both Independent review committee-assessed and investigator assessment

| | All randomised (ITT) | Excluding patients that received AVE post-progression |
|----------------------------|----------------------|---|
| Cohort | AVE + BSC (N=350) | AVE + BSC (N=230) |
| Subjects with event, n (%) | 145 (41.4) | 83 (36.1) |
| Median OS, months (95% CI) | 21.4 (18.9, 26.1) | 26.0 (22.5, NE) |
| Stratified HR (95% CI) | 0.69 (0.556, 0.863) | 0.64 (0.494, 0.833) |
| 1-sided p-value | 0.0005 | 0.0004 |

Source: Table 1 of PSCR

- 6.25 Table 8 presents the results for independent review committee and investigator-assessed best overall response for the JAVELIN Bladder 100 trial.

Public Summary Document– March 2021 PBAC Meeting

Table 8: Best overall response results for the JAVELIN Bladder 100 trial

| Cohort | AVE + BSC (N=350) | BSC (N=350) |
|--|-----------------------|--------------------|
| Median duration of follow-up, months (range) | 19.6 (18.0 - 20.6) | 19.2 (17.4 - 21.6) |
| Independent review committee-assessed | | |
| Best overall response, n (%) | | |
| - Complete response | 21 (6.0) | 3 (0.9) |
| - Partial response | 13 (3.7) | 2 (0.6) |
| - Stable disease | 44 (12.6) | 46 (13.1) |
| - Non-CR/non-PD | 66 (18.9) | 45 (12.9) |
| - Progressive disease | 130 (37.1) | 169 (48.3) |
| - Not evaluable | 76 (21.7) | 85 (24.3) |
| Objective response (CR+PR), n (%) | 34 (9.7) | 5 (1.4) |
| Objective response, odds ratio (95% CI) | 7.464 (2.824, 24.445) | |
| Investigator-assessed | | |
| Best overall response, n (%) | | |
| - Complete response | 22 (6.3) | 5 (1.4) |
| - Partial response | 21 (6.0) | 7 (2.0) |
| - Stable disease | 78 (22.3) | 52 (14.9) |
| - Non-CR/non-PD | 57 (16.3) | 55 (15.7) |
| - Progressive disease | 102 (29.1) | 168 (48.0) |
| - Not evaluable | 70 (20.0) | 63 (18.0) |
| Objective response (CR+PR), n (%) | 43 (12.3) | 12 (3.4) |
| Objective response, odds ratio (95% CI) | 3.939 (1.989, 8.327) | |

Source: Table 2.5-4, p72 of the submission; Table 17, pp75-76 of Appendix 1A of the submission; Table 14.2.1.1, pp11-13 of Appendix 1C of the submission.

Abbreviations: AVE, avelumab; BSC, best supportive care; CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response.

- 6.26 Based on the independent review committee-assessed outcomes, the overall response rate was statistically significantly higher in the avelumab + BSC arm (9.7%) compared to the BSC arm (1.4%; odds ratio 7.46, 95% CI: 2.82-24.44).
- 6.27 Results based on investigator-assessed outcomes were generally consistent with the independent review committee-assessed results, with slightly higher proportions of patients achieving objective responses in each arm (12.3% in the avelumab + BSC arm versus 3.4% in the BSC arm; odds ratio 3.94 [95% CI: 1.99-8.33]).
- 6.28 Table 9 presents the results of patient reported outcomes in the JAVELIN Bladder 100 trial.

Table 9: Patient reported outcomes reported in the JAVELIN Bladder 100 trial

| | AVE + BSC | BSC | AVE + BSC vs BSC Mean difference (95% CI) |
|--|----------------------|----------------------|---|
| Functional Assessment of Cancer Therapy Bladder Cancer Symptom Index-18 (FACT FBISI-18) | | | |
| Baseline, mean (SD) | N=332 53.3 (9.59) | N=329 52.7 (9.31) | |
| Overall treatment, mean (95% CI) | 52.51 (51.54, 53.48) | 52.41 (51.23, 53.59) | 0.099 (-1.429, 1.627) |
| EuroQoL 5-dimension 5-level (EQ-5D-5L) | | | |
| Baseline, mean (SD) | N=336 0.81 (0.18) | N=327 0.79 (0.20) | |
| Overall treatment, mean (95% CI) | 0.77 (0.75, 0.79) | 0.75 (0.73, 0.78) | 0.014 (-0.020, 0.048) |

Source: Table 2.5-8, p77 of the submission; Table 14.5.2.2.2.2, p31; Table 14.5.2.3.2.4, p97 of the clinical study report, Appendix 1D of the submission.

Abbreviations: AVE, avelumab; BSC, best supportive care; CI, confidence interval; EQ-5D-5L, EuroQoL 5-dimension 5-level; FBISI, Functional Assessment of Cancer Therapy Bladder Cancer Symptom Index-18; SD, standard deviation.

6.29 There were no statistically significant differences between treatment arms for the FACT FBISI-18 or EQ-5D-5L at any of the assessed time points, or for the overall treatment comparisons.

Subgroup analyses

6.30 Among patients with PD-L1 positive tumours at baseline, treatment with avelumab + BSC was associated with a statistically significant increase in overall survival compared to treatment with BSC (median overall survival not reached for avelumab + BSC versus 17.1 months for BSC; hazard ratio: 0.56 [95% CI: 0.40-0.79]). Among patients with PD-L1 negative tumours at baseline, treatment with avelumab + BSC was associated with an increase in overall survival compared to treatment with BSC but the difference was not statistically significant (median overall survival 18.8 months for avelumab + BSC versus 13.7 months for BSC; hazard ratio: 0.85 [95% CI: 0.62-1.18]). A test for interaction for the subgroup of patients with PD-L1 negative tumours versus PD-L1 positive tumours was not statistically significant ($p = 0.0803$). The pre-PBAC response argued that, while not statistically significant, the incremental improvement in median overall survival of 5.1 months reported in PD-L1 negative patients was clinically meaningful.

6.31 Among patients with PD-L1 positive tumours at baseline, treatment with avelumab + BSC was associated with a statistically significant increase in progression-free survival compared to treatment with BSC alone (median progression-free survival 5.7 months for avelumab + BSC versus 2.1 months for BSC; hazard ratio: 0.56 [95% CI: 0.43, 0.73]). Among patients with PD-L1 negative tumours at baseline, treatment with avelumab + BSC was also associated with a statistically significant increase in progression-free survival compared to treatment with BSC alone (median progression-free survival 3.0 months for avelumab + BSC versus 1.9 months for BSC; hazard ratio: 0.63 [95% CI: 0.47, 0.84]). A test for interaction for the subgroup of patients with PD-L1 negative tumours versus PD-L1 positive tumours was not statistically significant ($p = 0.5204$).

Comparative harms

6.32 Table 10 summarises the results of safety outcomes for the JAVELIN Bladder 100 trial during the on-treatment period (median follow-up 19.6 months for the avelumab + BSC arm, 19.2 months for the BSC arm). The results should be interpreted with caution given that the JAVELIN Bladder 100 trial was an open-label trial, and the BSC arm did not include any active anticancer treatment during the on-treatment period.

Table 10: Summary of key adverse events in the JAVELIN Bladder 100 trial (on-treatment period)

| Trial ID | AVE + BSC n (%) | BSC n (%) | AVE + BSC vs BSC RD (95% CI) |
|---------------------------------------|--------------------|--------------|---------------------------------|
| Any AE | 337 (98.0) | 268 (77.7) | 0.20 (0.16, 0.25) |
| Grade ≥3 AE | 163 (47.4) | 87 (25.2) | 0.22 (0.15, 0.29) |
| Treatment-related AE | 266 (77.3) | 4 (1.2) | 0.76 (0.72, 0.81) |
| Treatment-related AE Grade ≥3 | 57 (16.6) | 0 | 0.17 (0.13, 0.20) |
| Treatment-related AE leading to death | 1 (0.3) | 0 | 0.006 (-0.004, 0.016) |
| Immune-related AEs | 101 (29.4) | 5 (1.4) | 0.28 (0.23, 0.33) |
| AE leading to discontinuation | 41 (11.9) | 0 | 0.12 (0.08, 0.15) |
| Grade ≥3 AE in >1% | | | |
| - Urinary tract infection | 15 (4.4) | 9 (2.6) | 0.02 (-0.01, 0.04) |
| - Anaemia | 13 (3.8) | 10 (2.9) | 0.01 (-0.02, 0.04) |
| - Fatigue | 6 (1.7) | 2 (0.6) | 0.01 (-0.004, 0.03) |
| - Haematuria | 6 (1.7) | 5 (1.4) | 0.00 (-0.02, 0.02) |
| - Back pain | 4 (1.2) | 8 (2.3) | -0.01 (-0.03, 0.01) |
| - Vomiting | 4 (1.2) | 2 (0.6) | 0.01 (-0.01, 0.02) |
| - Asthenia | 0 | 4 (1.2) | -0.01 (-0.02, 0.001) |

Source: Table 2.5-5, p.74 of the submission.

Abbreviations: AE, adverse event; AVE, avelumab; BSC, best supportive care; RD, risk difference.

- 6.33 Ninety-eight percent of patients in the avelumab + BSC arm experienced at least one treatment-emergent adverse event, compared to 78% of patients in the BSC arm. The most commonly reported treatment-emergent adverse events in the avelumab + BSC arm (>15%) were fatigue, pruritus, urinary tract infection, diarrhoea, arthralgia, asthenia, constipation, back pain, and nausea.
- 6.34 Seventy-seven percent of patients in the avelumab + BSC arm reported at least one treatment-related adverse event, compared to 1.2% in the BSC arm. Grade ≥3 adverse events (>1%) in the avelumab + BSC arm included urinary tract infection (4.4%), anaemia (3.8%), fatigue (1.7%), haematuria (1.7%) and back pain (1.2%).
- 6.35 Fatal treatment-emergent adverse events were reported in 1.2% of patients treated with avelumab + BSC and 7.0% of patients treated with BSC alone. Two patients in the avelumab + BSC arm had a fatal adverse event that was considered related to treatment, including one event of sepsis, and one event of ischemic stroke that occurred 100 days after a single dose of avelumab.
- 6.36 Immune-related adverse events were reported for 29.4% of patients in the avelumab + BSC arm and 1.4% of patients in the BSC alone arm. In the avelumab + BSC arm, immune-related Grade 3 events were reported for 7.0% of patients and no Grade 4 or Grade 5 events were reported. In the avelumab + BSC arm, the highest frequency of immune-related adverse events was in the thyroid disorders cluster (12.2%), and the

most common immune-related adverse events were hypothyroidism (10.2%), rash (4.9%), and hyperthyroidism (4.7%). Nineteen (5.5%) patients in the avelumab + BSC arm discontinued study treatment due to an immune-related adverse event.

Benefits/harms

6.37 A summary of the comparative benefits and harms for avelumab + BSC versus BSC is presented in the table below.

Table 11: Summary of the comparative benefits and harms for avelumab + BSC versus BSC

| Benefits | | | | | | |
|---|-------------------|------------|----------------------|-------------------------|---------------------|-----------------------|
| | AVE + BSC | | BSC | Absolute difference | HR (95% CI) | |
| Progression-free survival (median duration of follow-up 19 months)¹ | | | | | | |
| Disease progression or death, n (%) | 225 (64.3) | | 260 (74.3) | -10.0% | 0.62 (0.519, 0.751) | |
| Median PFS, months (95% CI) | 3.7 (3.5, 5.5) | | 2.0 (1.9, 2.7) | 1.7 months | | |
| Not progressed at 6 months, % (95% CI) | 40.7 (35.2, 46.1) | | 21.8 (17.2, 26.7) | 18.9% | | |
| Not progressed at 12 months, % (95% CI) | 29.6 (24.4, 35.0) | | 13.1 (9.2, 17.8) | 16.5% | | |
| Overall survival (median duration of follow-up 19 months) | | | | | | |
| Death, n/N (%) | 145 (41.4) | | 179 (51.1) | -9.7% | 0.69 (0.556, 0.863) | |
| Median OS, months (95% CI) | 21.4 (18.9, 26.1) | | 14.3 (12.9, 17.9) | 7.1 months | | |
| Alive at 12 months, % (95% CI) | 71.3 (66.0, 76.0) | | 58.4 (52.7, 63.7) | 12.9% | | |
| Alive at 24 months, % (95% CI) | 48.1 (41.3, 54.7) | | 37.2 (30.9, 43.4) | 10.9% | | |
| Harms | | | | | | |
| Event | AVE + BSC n/N | BSC n/N | RR (95% CI) | Event rate/100 patients | | RD (95% CI) |
| | | | | AVE + BSC | BSC | |
| Grade ≥3 urinary tract infection | 15/344 | 9/345 | 1.67 (0.74, 3.77) | 4.4 | 2.6 | 0.02 (-0.01, 0.04) |
| Grade ≥3 anaemia | 13/344 | 10/345 | 1.30 (0.58, 2.93) | 16.2 | 14.5 | 0.01 (-0.02, 0.04) |

Source: Table 2.5-1, p63; Table 2.5-2, p67; Table 2.5-6, p75 of the submission. Table 13, pp62-63 of the JAVELIN Bladder 100 clinical study report, Appendix 1A of the submission.

Abbreviations: AVE, avelumab; BSC, best supportive care; CI, confidence interval; OS, overall survival; PFS, progression-free survival; RD, risk difference; RR, risk ratio.

¹ Progression-free survival assessed by independent review committee.

6.38 On the basis of the direct evidence presented in the submission, for every 100 patients treated with avelumab + BSC in comparison with BSC alone:

- Approximately 11 additional patients will remain alive at two years.
- Approximately 17 additional patients will remain free of disease progression at 12 months.
- Approximately 2 additional patients will experience a life-threatening or severe urinary tract infection.
- Approximately 1 additional patient will experience a life-threatening or severe anaemia.

Clinical claim

6.39 Based on the direct comparison of avelumab + BSC versus BSC in the JAVELIN Bladder 100 trial, the submission described avelumab + BSC as superior in terms of overall survival and progression-free survival, and inferior in terms of safety compared to BSC.

The evaluation suggested the following issues should be considered when interpreting the clinical claims:

- In the full trial population, and among the subgroup of patients with PD-L1 positive tumours, treatment with avelumab + BSC was associated with statistically significant improvements in overall survival and progression-free survival compared to BSC. In the subgroup of patients with PD-L1 negative tumours at baseline, treatment with avelumab + BSC was associated with an increase in overall survival compared to treatment with BSC, but the difference was not statistically significant. The ESC considered the benefit of avelumab on overall survival in PD-L1 negative patients is therefore unclear.
- Overall survival results are likely to have been impacted by differences in the pattern of use of subsequent anticancer therapies between treatment arms. The ESC considered the use of subsequent anticancer treatments in the BSC arm of the JAVELIN Bladder 100 trial is lower than the expected use of subsequent anticancer treatment in Australian clinical practice. The ESC considered the significant overall survival results of the JAVELIN Bladder 100 trial should be interpreted with caution given overall survival in the BSC arm was potentially underestimated as a result of a lower proportion of patients receiving subsequent treatment with a PD-1/PD-L1 inhibitor than would be expected in the Australian setting. The pre-PBAC response presented an ad-hoc analysis of overall survival for three sub-groups of the BSC arm of the JAVELIN Bladder 100 trial (see paragraph 6.17).
- Treatment with avelumab + BSC was associated with statistically significantly higher rates of treatment-emergent adverse events, Grade ≥ 3 adverse events, treatment-related adverse events and immune-related adverse events.
- There is a lack long-term efficacy and safety data for avelumab.

6.40 As outlined in paragraph 5.3, the ESC considered an appropriate comparator may be BSC and subsequent therapy with pembrolizumab, as per current Australian clinical practice. The ESC advised that the JAVELIN Bladder 100 trial does not provide a comparison of the effectiveness of maintenance avelumab + BSC and BSC + pembrolizumab use on progression. The ESC noted the median progression-free survival reported in the BSC arm of the JAVELIN Bladder 100 trial was 2.0 months. The ESC considered it was unknown whether there is a clinical benefit of receiving maintenance avelumab + BSC over BSC + pembrolizumab use on progression.

6.41 The PBAC considered that the claim of superior comparative effectiveness to BSC was reasonable and adequately supported by the data in terms of overall survival, although the Committee acknowledged there was some uncertainty in the PD-L1 negative subgroup. The PBAC considered that, although the overall survival data presented supported the claim of superior comparative effectiveness versus BSC, the small median PFS benefit reported highlighted the importance of subsequent anticancer therapies. The PBAC considered it reasonable to anticipate that maintenance avelumab would offer benefit to some patients versus waiting for

disease progression to initiate second-line pembrolizumab, although the magnitude of the incremental benefit is uncertain.

- 6.42 The PBAC considered that the claim of inferior comparative safety to BSC was reasonable and adequately supported by the data. The PBAC considered that the safety of avelumab + BSC compared to BSC + pembrolizumab use on progression would likely be non-inferior.

Economic analysis

- 6.43 The submission presented a stepped economic evaluation of avelumab + BSC compared to BSC alone, in patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed following treatment with first-line platinum-based chemotherapy. The type of economic evaluation was a cost-utility analysis.

Public Summary Document– March 2021 PBAC Meeting

Table 12: Summary of model structure and key inputs

| Component | Summary |
|----------------------------------|---|
| Treatments | Avelumab + BSC versus BSC |
| Time horizon | 10 years in the model base case versus median duration of follow-up of 19 months in the JAVELIN Bladder 100 trial. |
| Outcomes | Life-years gained; quality-adjusted life years. |
| Methods used to generate results | Partitioned survival analysis |
| Health states | Progression-free, progressive disease and dead. |
| Cycle length | 7 days |
| Allocation to health states | Extrapolated overall survival and progression-free survival curves based on data from the JAVELIN Bladder 100 trial. |
| Extrapolation method | <p>Overall survival: Extrapolated using a generalised gamma function fitted to JAVELIN Bladder 100 trial data for the avelumab + BSC and BSC arms.</p> <p>Progression-free survival: Extrapolated using piecewise functions fitted to JAVELIN Bladder 100 trial data (avelumab + BSC: Gompertz function for initial 8 weeks and Weibull function beyond 8 weeks; BSC: Gompertz function for initial 8 weeks and log-normal function beyond 8 weeks).</p> <p>Time to treatment discontinuation: Extrapolated using a generalised gamma function for the avelumab + BSC arm, and a log-logistic function for the BSC arm.</p> <p>51% of the incremental QALYs and 31% of the incremental costs are accrued in the extrapolated period.</p> |
| Health related quality of life | Progression-free state: 0.772; progressed disease state: 0.698; Death: 0. Based on EQ-5D-5L results from the JAVELIN Bladder 100 trial mapped to EQ-5D-3L using a crosswalk algorithm (van Hout et al., 2012) and the value set for EQ-5D-3L derived weights for England (Dolan 1997). |
| Health resource use and costs | <p>Duration of avelumab treatment based on drug exposure reported in the JAVELIN Bladder 100 trial (extrapolated time to treatment discontinuation curve).</p> <p>Disease monitoring costs for the progression-free and progressive disease states derived from a survey of 11 Australian oncologists with expertise in the management of patients with locally advanced and metastatic urothelial carcinoma (conducted by the sponsor).</p> <p>Included costs associated with the management of Grade ≥ 3 adverse events that occurred in at least 2% of patients, and all Grade ≥ 3 immune-related adverse events in the JAVELIN Bladder 100 trial. Costs estimated by mapping of adverse events to AR-DRGs.</p> <p>Costs of subsequent anticancer treatments based on the proportions of patients using subsequent anticancer treatments in the JAVELIN Bladder 100 trial, adapted to the Australian treatment setting based on input from clinicians and additional sponsor assumptions. The submission estimated the pembrolizumab effective price by applying a 10% discount to the published pembrolizumab AEMP.</p> |

Source: Table 3.1-1, p99; Section 3.4, pp122-139; Section 3.4.5, pp138-139; Table 3.5-1, p140; Section 3.6, pp140-153 of the submission. Abbreviations: AR-DRG, Australian-refined diagnosis-related groups; BSC, best supportive care; EQ-5D, EuroQol 5-Dimension.

6.44 The ESC noted the economic model was based on the results of the JAVELIN Bladder 100 trial. The JAVELIN Bladder 100 trial recruited patients with documented Stage IV disease, which differed from the proposed PBS population (patients with Stage III and Stage IV disease).

- 6.45 The base case analysis employed a 10-year time horizon with a one-week cycle length. The submission claimed that the use of a 10-year time horizon was supported by reported survival outcomes for patients with locally advanced and metastatic urothelial carcinoma in the published literature. The extrapolation of overall survival and progression-free survival from 33 months using parametric functions fitted to Kaplan-Meier curves from the JAVELIN Bladder 100 trial was associated with substantial uncertainty. In the July 2018 consideration of pembrolizumab for urothelial cancer, the PBAC considered that a 5-year time horizon was appropriate given the short life-expectancy in the target population and that benefits in urothelial cancer are derived within the first 5 years of treatment (paragraph 7.15, pembrolizumab public summary document, July 2018 PBAC meeting). The PSCR argued that it was appropriate to assume a time horizon longer than the 5 years in the pembrolizumab submission given the prognosis of patients for whom listing of avelumab is sought is likely to be better than those who are eligible for treatment with pembrolizumab. The ESC considered that a time horizon of 7.5 years may be appropriate. The pre-PBAC response noted that the ICER does not change substantially between analyses based on time horizons of 7.5 years (\$55,000 to < \$75,000/QALY) and 10 years (\$55,000 to < \$75,000/QALY).
- 6.46 The economic model included costs associated with the intervention medicines (avelumab), disease monitoring, adverse event management, and subsequent anticancer therapies.
- 6.47 The number of scripts for avelumab was based on exposure data from the JAVELIN Bladder 100 trial (extrapolated time to treatment discontinuation curve). The evaluation noted this may have overestimated the costs associated with avelumab, given that a proportion of patients in the JAVELIN Bladder 100 trial received treatment with avelumab beyond disease progression. Best supportive care was assumed to have no cost.
- 6.48 The resource requirements associated with disease monitoring were derived from a survey of 11 Australian oncologists with expertise in the management of patients with locally advanced and metastatic urothelial carcinoma (conducted by the sponsor). The applicability of the survey results was unclear, as there were few details provided on the surveyed specialists or the characteristics of the treated patients. Costs of disease monitoring were higher in the progressed disease health state (\$263.66 per cycle) compared to the progression-free health state (\$186.14 per cycle).
- 6.49 The economic model included costs associated with the management of Grade ≥ 3 adverse events that occurred in at least 2% of patients, and all Grade ≥ 3 immune-related adverse events in the JAVELIN Bladder 100 trial. The restriction to adverse events of Grade ≥ 3 in at least 2% of patients is likely to favour the avelumab + BSC arm, given that the BSC arm did not include any active anticancer treatment. The submission did not adequately justify the use of incidence estimates rather than event rates given the potential for patients to experience multiple events, and the extrapolation of avelumab time on treatment beyond the duration of the trial.

- 6.50 The submission stated that the cost of subsequent anticancer treatment was based on the subsequent anticancer treatments used in the JAVELIN Bladder 100 trial, adapted to the Australian treatment setting based on input from clinicians and sponsor assumptions. Patients in the avelumab + BSC arm who experience disease progression are assumed to receive paclitaxel (60%), docetaxel (15%) or no treatment (36%). The assumption that all patients treated with chemotherapy would receive paclitaxel or docetaxel was not adequately justified, given that some patients in the JAVELIN Bladder 100 trial were also treated with gemcitabine, cisplatin, and carboplatin, and PD-1/PD-L1 inhibitors. A higher proportion of patients in the avelumab + BSC arm were assigned 'no treatment' as subsequent treatment, which did not appear to be adequately justified, given that most patients would be expected to experience disease progression over the 10-year time horizon.
- 6.51 The submission assumed that 80% of patients who experience disease progression in the BSC arm commence subsequent treatment with a PD-1 inhibitor, and the remaining patients were distributed between chemotherapy and no subsequent anticancer treatment. This assumption resulted in inconsistency between the costs for pembrolizumab included in the model, and the underlying use (and effectiveness) of the subsequent therapies used in the JAVELIN Bladder 100 trial. At the time of the interim analysis, 43.7% of all patients in the BSC arm had received subsequent treatment with a PD-1 or PD-L1 inhibitor. The higher cost of the subsequent therapy mix assumed for the BSC arm was likely to favour avelumab + BSC. The PSCR highlighted that the cost of subsequent anticancer treatments in the model was based on the count of the number of patients who received each type of subsequent treatment in the JAVELIN Bladder 100 trial, although this was subsequently proportionally adjusted to reflect the distribution of use in Australian clinical practice. The ESC noted that all use of PD-1/PD-L1 inhibitors as subsequent treatment in the model was as a proportion of patients who have progressed. The ESC noted that in the JAVELIN Bladder 100 trial, 61% (153/251) of patients who experienced disease progression in the BSC arm received subsequent treatment with a PD-1/PD-L1 inhibitor which is lower than the 80% assumed in the model. The ESC noted that no adjustment was made in the model to the overall survival data to account for difference in the proportion of patients receiving PD-1/PD-L1 inhibitors in the trial versus that assumed in the model. As such, the ESC considered there were higher costs associated with PD-1/PD-L1 inhibitor therapy in the BSC arm of the model without corresponding adjustments to efficacy outcomes. The ESC considered this favoured avelumab. The pre-PBAC response stated that although overall survival for the BSC arm of the model was not adjusted for the greater proportion of use of subsequent treatment with a PD-1/PD-L1 inhibitor, the result of the ad-hoc analysis of the BSC arm subgroups (see paragraph 6.17) indicated that patients who received subsequent treatments with a PD-1/PD-L1 inhibitor experienced a small improvement in overall survival (approximately 2.5 months).

6.52 The submission noted that the proportions of patients receiving subsequent anticancer treatment sum to more than 100% (110% in avelumab + BSC arm and 125.5% in BSC arm) due to some patients receiving more than one subsequent anticancer therapy in the JAVELIN Bladder 100 trial. The assumed proportions may not have adequately captured the costs associated with patients receiving multiple lines of subsequent anticancer treatment over the modelled period. The ESC noted the costs assumed for subsequent anti-cancer therapy in the model were considered highly uncertain due to missing data on subsequent therapies for a large number of patients, limited duration of follow-up in the trial, and the likelihood that some patients will receive multiple lines of subsequent therapy. The submission noted that pembrolizumab is subject to a special pricing arrangement and that the effective price is not known to the sponsor. The submission estimated the effective pembrolizumab price by applying a 10% discount to the published pembrolizumab ex-manufacturer price.

6.53 Key drivers of the economic model are summarised in the table below.

Table 13: Key drivers of the model

| Description | Method/Value | Impact |
|----------------------------------|---|----------------------------|
| Extrapolation | Overall survival and progression-free survival data from the JAVELIN Bladder 100 trial were extrapolated using parametric functions. Extrapolation of the survival curves using parametric functions was associated with substantial uncertainty due to the limited duration of trial follow-up relative to the time horizon (median 19 months follow-up versus 10-year time horizon), and the lack of published longer-term survival estimates to validate the chosen parametric functions. | High, direction unclear |
| Subsequent anticancer treatments | The cost of subsequent treatments was based on the subsequent anticancer treatments used in the JAVELIN Bladder 100 trial, adapted to the Australian treatment setting based on input from clinicians and sponsor assumptions. The costs assumed for subsequent anti-cancer therapy in the model were considered highly uncertain due to missing data on subsequent therapies for a large number of patients, the limited duration of follow-up, and the likelihood that many patients will receive multiple lines of subsequent therapy. There was potential inconsistency between the costs assumed in the economic model and the underlying use (and effectiveness) of the subsequent therapies in the JAVELIN Bladder 100 trial. In particular, the submission assumed that 80% of patients in the BSC arm with disease progression receive treatment with pembrolizumab. However, at the time of the interim analysis, only 43.7% of all patients in the BSC arm (or 61% of patients who had experienced disease progression) had received subsequent treatment with a PD-1 or PD-L1 inhibitor. The higher cost of the subsequent therapy mix assumed for the BSC arm was likely to favour the avelumab + BSC. | Moderate, favours avelumab |

Source: Constructed during the evaluation.

Abbreviations: BSC, best supportive care; EQ-5D, EuroQol 5-Dimension.

6.54 The results of the modelled economic evaluation are summarised below.

Table 14: Results of the stepped economic evaluation

| Step and component | AVE + BSC | BSC | Increment |
|--|---------------|----------|----------------------------|
| Step 1: Trial-based analysis of life-years gained over 33 months, including avelumab treatment costs only (drug and administration) | | | |
| Costs | \$ [REDACTED] | \$0 | \$ [REDACTED] |
| Life years | 1.74 | 1.45 | 0.29 |
| Incremental cost/extra life year gained | | | \$ [REDACTED] ¹ |
| Step 2: Time horizon increased to 10 years | | | |
| Costs | \$ [REDACTED] | \$0 | \$ [REDACTED] |
| Life years | 2.75 | 2.14 | 0.61 |
| Incremental cost/extra life year gained | | | \$ [REDACTED] ² |
| Step 3: Disease monitoring costs, adverse events costs, and subsequent anticancer treatment costs included | | | |
| Costs | \$ [REDACTED] | \$80,168 | \$ [REDACTED] |
| Life years | 2.75 | 2.14 | 0.61 |
| Incremental cost/extra LYG gained | | | \$ [REDACTED] ³ |
| Step 4: Health state utility weights applied | | | |
| Costs | \$ [REDACTED] | \$80,168 | \$ [REDACTED] |
| QALYs | 2.02 | 1.55 | 0.47 |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] ⁴ |
| Step 5: Financial stopping rule included | | | |
| Costs | \$ [REDACTED] | \$80,168 | \$ [REDACTED] |
| QALYs | 2.02 | 1.55 | 0.47 |
| Incremental cost/extra QALY gained (base case) | | | \$ [REDACTED] ⁵ |

Source: Table 3.8-1, p160 of the submission.

Abbreviations: AVE, avelumab; BSC, best supportive care; LYG, life years gained; QALY, quality adjusted life year.

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000/QALY gained

² \$135,000 to < \$155,000/QALY gained

³ \$75,000 to < \$95,000/QALY gained

⁴ \$95,000 to < \$115,000/QALY gained

⁵ \$55,000 to < \$75,000/QALY gained

6.55 The difference in incremental cost between treatment arms was driven by the cost of avelumab, which was partially offset by costs associated with pembrolizumab as a subsequent anticancer treatment. The difference in health outcomes was primarily driven by the additional time spent in the progression-free health state, associated with better quality of life, for patients treated with avelumab + BSC, compared to BSC. The PBAC noted the BSC costs differed to those presented in Table 14 when the effective price of pembrolizumab was applied.

6.56 Based on the economic model presented in the submission, treatment with avelumab + BSC was associated with a cost per QALY gained of \$55,000 to < \$75,000 compared to BSC alone.

6.57 The results of key univariate sensitivity analyses are summarised below.

Public Summary Document– March 2021 PBAC Meeting

Table 15: Results of sensitivity analyses

| Analyses | Incremental cost | Incremental QALY | ICER |
|--|------------------|------------------|----------------------------|
| Base case | \$ [redacted] | 0.47 | \$ [redacted] ¹ |
| Time horizon (base case: 10 years) | | | |
| - 5 years* | \$ [redacted] | 0.36 | \$ [redacted] ² |
| - 7.5 years | \$ [redacted] | 0.43 | \$ [redacted] ¹ |
| Health state utilities (base case: PF 0.772; PD 0.698) | | | |
| - PF 0.678, PD 0.614 (SMC [1339/18]) | \$ [redacted] | 0.41 | \$ [redacted] ¹ |
| - PF 0.860, PD 0.810 (Srivastava et al., 2020) | \$ [redacted] | 0.52 | \$ [redacted] ¹ |
| Avelumab + BSC extrapolation for overall survival | | | |
| - Independent single fit – Exponential | \$ [redacted] | 0.44 | \$ [redacted] ¹ |
| - Independent single fit – Weibull | \$ [redacted] | 0.18 | \$ [redacted] ³ |
| - Independent single fit – Gompertz | \$ [redacted] | 0.22 | \$ [redacted] ⁴ |
| - Independent single fit – Log-Logistic | \$ [redacted] | 0.31 | \$ [redacted] ² |
| - Independent single fit – Log-Normal | \$ [redacted] | 0.38 | \$ [redacted] ¹ |
| BSC extrapolation for OS | | | |
| - Independent single fit – Exponential | \$ [redacted] | 0.53 | \$ [redacted] ¹ |
| - Independent single fit – Weibull | \$ [redacted] | 0.60 | \$ [redacted] ¹ |
| - Independent single fit – Gompertz | \$ [redacted] | 0.53 | \$ [redacted] ¹ |
| - Independent single fit – Log-Normal | \$ [redacted] | 0.55 | \$ [redacted] ¹ |
| - Independent single fit – Log-Logistic | \$ [redacted] | 0.59 | \$ [redacted] ⁶ |
| Adverse event costs* | | | |
| - Costs removed | \$ [redacted] | 0.47 | \$ [redacted] ¹ |
| - Double cost for avelumab + BSC | \$ [redacted] | 0.47 | \$ [redacted] ¹ |
| Disease monitoring costs* | | | |
| - Costs removed | \$ [redacted] | 0.47 | \$ [redacted] ⁶ |
| - PF cost same as PD cost | \$ [redacted] | 0.47 | \$ [redacted] ¹ |
| Subsequent treatment with PD-L1 (BSC arm)* | | | |
| - 100% | \$ [redacted] | 0.47 | \$ [redacted] ⁷ |
| - 90% | \$ [redacted] | 0.47 | \$ [redacted] ⁶ |
| - 70% | \$ [redacted] | 0.47 | \$ [redacted] ² |
| - 60% | \$ [redacted] | 0.47 | \$ [redacted] ² |
| Financial stopping rule (Base case: included)* | | | |
| - Excluded | \$ [redacted] | 0.47 | \$ [redacted] ⁵ |
| OS curve convergence (base case: no convergence)** | | | |
| - OS convergence from 5 to 10 years | \$ [redacted] | 0.47 | \$ [redacted] ¹ |
| - OS convergence from 7.5 to 10 years | \$ [redacted] | 0.46 | \$ [redacted] ¹ |
| - OS convergence from 5 to 7.5 years | \$ [redacted] | 0.41 | \$ [redacted] ¹ |
| Avelumab + BSC extrapolation for time to treatment discontinuation (base case: generalised gamma; mean duration of treatment 16.74 months)** | | | |
| - Exponential (mean treatment duration: 12.64 months) | \$ [redacted] | 0.47 | \$ [redacted] ¹ |
| - Weibull (mean treatment duration: 12.85 months) | \$ [redacted] | 0.47 | \$ [redacted] ¹ |
| - Log-normal (mean treatment duration: 14.90 months) | \$ [redacted] | 0.47 | \$ [redacted] ¹ |
| - Log-logistic (mean treatment duration: 15.77 months) | \$ [redacted] | 0.47 | \$ [redacted] ¹ |
| - Gompertz (mean treatment duration: 18.66 months) | \$ [redacted] | 0.47 | \$ [redacted] ¹ |

Source: Table 3.9-1, pp163-164 of the submission; *constructed during the evaluation using the 'Bavencio (avelumab) Economic Evaluation' Excel workbook. **constructed during the ESC evaluation using the 'Bavencio (avelumab) Economic Evaluation' Excel workbook.

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PD, progressive disease; OS, overall survival; PF, progression-free; PFS, progression-free survival; QALY, quality adjusted life year; SMC, Scottish Medicines Consortium; TTD, time to treatment discontinuation.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000/QALY gained

² \$75,000 to < \$95,000/QALY gained

³ \$135,000 to < \$155,000/QALY gained

Public Summary Document– March 2021 PBAC Meeting

⁴ \$115,000 to < \$135,000/QALY gained

⁵ \$95,000 to < \$115,000/QALY gained

⁶ \$45,000 to < \$55,000/QALY gained

⁷ \$35,000 to < \$45,000/QALY gained

- 6.58 The results of sensitivity analyses indicate that the model is most sensitive to a reduction in the model time horizon, the choice of parametric extrapolation for overall survival for the avelumab + BSC arm, and the proportion of patients in the BSC arm receiving pembrolizumab as a subsequent anticancer treatment.
- 6.59 The ESC considered that overall survival curve convergence would be appropriate to reflect the likely reduction in treatment benefits of avelumab over time. The ESC noted that overall survival curve convergence from 5 years to 7.5 years increased the ICER to \$55,000 to < \$75,000 per QALY.
- 6.60 The ESC noted the base case scenario included the proposed financial stopping rule where the cost of avelumab incurred after the fourth year of treatment would be provided as a rebate to government. The ESC noted this had a substantial effect on the ICER, which increased from \$55,000 to < \$75,000 per QALY (base case) to \$95,000 to < \$115,000 per QALY when the stopping rule was removed. As outlined in paragraph 6.70, the ESC and DUSC considered the proposed four year stopping rule inappropriate.
- 6.61 In the economic model, costs associated with avelumab treatment were estimated by fitting parametric functions to the time to treatment discontinuation data reported for the JAVELIN Bladder 100 trial. In the base case, Kaplan-Meier data for the avelumab + BSC arm were extrapolated using a generalised gamma function, resulting in a mean treatment duration of 16.74 months. The PSCR argued the extrapolation must be considered in the context of the observed Kaplan-Meier survival rather than based on a comparison of median follow-up versus the time horizon. The ESC considered the choice of extrapolation functions in the submission was not adequately justified. The ESC advised that the alternative extrapolation functions presented in the sensitivity analyses could be used to explore the impact of different mean treatment durations (see Table 15). However, the ESC noted that time to treatment discontinuation in the model was independent of health outcomes (i.e. affects avelumab drug costs only), and therefore the sensitivity analyses above do not capture the impact of differences in treatment duration on clinical outcomes. The PBAC noted that extrapolation of the time to treatment discontinuation with the generalised gamma function resulted in a proportion of patients being on treatment for a very long duration with 12%, 4% and 3% on treatment at 5, 7.5 and 10 years, respectively. The PBAC considered that a more appropriate approach to the extrapolation of time to treatment discontinuation for avelumab + BSC would be use of an exponential function for which the resulting mean treatment duration was 12.64 months with only 1% of patients remaining on treatment at 5 years.

Drug cost/patient/course

6.62 The estimated drug cost per patient for avelumab is \$ [REDACTED], based on the requested effective DPMA of \$ [REDACTED], assuming a 24.4% public/75.6% private split (based on pembrolizumab dispensing PBS data (October 2019 to September 2020), a dose of 800 mg every 2 weeks, 100% compliance with treatment and the treatment duration from the economic model base case of 16.74 months. The approach to estimating the cost of avelumab was consistent across the economic analysis and financial estimates.

Estimated PBS usage & financial implications

6.63 The submission was considered by DUSC.

6.64 The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with the PBS listing of avelumab for the proposed indication.

Table 15: Key inputs for the financial estimates

| Parameter | Value applied and source | Comment |
|---|--|---|
| Urinary tract cancer incidence per 100,000 (2021 to 2026) | Bladder: 12.09 to 12.59; Renal pelvis: 1.14 to 1.01; Ureter: 0.50 to 0.40; Urethral: 0.25 to 0.27. The historical incidence rate per 100,000 was estimated for each year by dividing the number of cases reported by the AIHW (bladder cancer: Cancer Data in Australia, 2020; renal pelvis, ureter, urethral: 2016 Australian Cancer Database pivot table) by the Australian population estimate. A linear trend line was fitted to the historical data to estimate the incidence rate of bladder cancer in each year over the period 2021 to 2026. | The evaluation considered the approach taken in the submission appeared reasonable. |
| Proportion of bladder cancer that is urothelial carcinoma | 93.7%; weighted average proportion weighted by sample size across 6 studies (Martin et al., 2020; Deuker et al., 2020; Abdel-Rahman, 2017a); Abdel-Rahman, 2017b; Patel et al., 2015; Boustead et al., 2014). | The evaluation considered the estimate appeared reasonable. |
| Proportion of urethral cancer that is urothelial carcinoma | 42%; Surveillance, Epidemiology, and End Results (SEER) registry in the years between 2004 and 2010 (Aleksic et al., 2018). | The evaluation considered the estimate appeared reasonable. |
| Proportion of renal pelvis and ureter cancer that is urothelial carcinoma | 87%; Population-based cancer registry in Denmark (Wihlborg et al., 2010). | The evaluation considered the estimate appeared reasonable. |
| Bladder cancer TNM distribution at diagnosis | Average proportion weighted by sample size across 5 studies (Boustead et al., 2013; Deuker et al., 2020; Danforth et al., 2020; Niu et al., 2012; and David et al., 2009). | The evaluation considered the estimate appeared reasonable. |
| Renal pelvis, ureter and urethra cancer TNM distribution at diagnosis | Derived from a study of patients diagnosed between 1997 and 2000 in the US National Cancer Data Base (NCDB; David et al., 2009). | The evaluation considered the estimate appeared reasonable. |
| Progression to LA & mUC from Tis/Ta/T1 N0 M0 or T2 N0 M0 | Yr1: 3%; Yr2: 5%; Yr3: 7%; Yr4: 9%; Yr5-6: 10%; Yr7: 11%; Yr8-9: 12%; Yr10: 13%. Average proportion weighted by sample size across 6 studies: Klatte et al. (2014); Pan et al. (2014); Bosset et al. (2015); Sylvester et al. (2006); Cambier et al. (2016); Fernandez-Gomez et al. (2009). | The evaluation considered the approach taken in the submission appeared reasonable. |

Public Summary Document– March 2021 PBAC Meeting

| Parameter | Value applied and source | Comment |
|---|--|---|
| Proportion of patients receiving first-line platinum-containing chemotherapy | 90%; clinician opinion. The submission also provided a literature-based estimate of 60% based on the weighted average of estimates from Barmias et al. (2018) and Sonpavde et al. (2012). | The evaluation considered the proportion of patients treated with first line platinum-containing chemotherapy was uncertain. |
| Proportion of patients free of disease progression post first-line platinum-containing chemotherapy | 75%; clinician opinion. The submission also provided a literature-based estimate of 60% based on the weighted average of estimates from Barmias et al. (2013), Bellmont et al. (2012), Krege et al. (2014), Miller et al. (2016), Hussain et al. (2014) and Sternberg et al. (2013). | The evaluation considered the proportion uncertain given that no time parameters are specified in the proposed restriction. |
| Uptake rate | Yr 1: 65%; Yr 2: 90%; Yr 3: 95%; Yr 4: 95%; Yr 5: 95%; Yr 6: 95%. Based on sponsor assumption. | The evaluation considered that uptake may be higher than estimated in Year 1 given that avelumab is recommended in treatment guidelines. |
| Patients receiving subsequent treatments | Avelumab listed: Yr 1: 69.9%; Yr 2: 8.3%; Yr 3: 5.6%; Yr 4: 3.5%; Yr 5: 2.4%; Yr 6: 1.8%. Avelumab not listed: Yr 1: 86.9%; Yr 2: 3.4%; Yr 3: 2.3%; Yr 4: 1.4%; Yr 5: 0.9%; Yr 6: 0.7%. Based outputs from the economic model | The evaluation considered the model outputs lacked applicability as they were based on the results of the JAVELIN Bladder 100 trial, which recruited patients with Stage IV disease only. |
| Subsequent treatments | Avelumab listed: pembrolizumab: 0%; paclitaxel: 60%; docetaxel: 15% Avelumab not listed: pembrolizumab: 80%; paclitaxel: 28%; docetaxel: 7%. Based on JAVELIN BLADDER 100 trial adapted to Australian setting based on clinician opinion and sponsor assumption. | The evaluation considered it unclear if adequately reflects treatments in Australian clinical practice. Patients may also be retreated with platinum-based chemotherapy. |

Source: Table 4.1-1, pp167-169 of the submission.

Abbreviations: ABS, Australian Bureau of Statistics; DPMA, dispensed price for maximum quantity; TNM, tumour, node, metastasis; Yr, Year.

6.65 Table 16 presents the estimated net cost to the PBS/RPBS of listing avelumab for the proposed indication.

Public Summary Document– March 2021 PBAC Meeting

Table 16: Estimated net cost to the PBS/RPBS of listing of avelumab

| | Year 1 (2021) | Year 2 (2022) | Year 3 (2023) | Year 4 (2024) | Year 5 (2025) | Year 6 (2026) |
|--|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Total eligible patients | █ ³ | █ ³ | █ ³ | █ ³ | █ ³ | █ ³ |
| Uptake rate | 65% | 90% | 95% | 95% | 95% | 95% |
| Initiating patients | █ ³ | █ ³ | █ ³ | █ ³ | █ ³ | █ ³ |
| Grandfathered patients | █ ³ | █ ³ | █ ³ | █ ³ | █ ³ | █ ³ |
| Total initiating patients | █ ³ | █ ³ | █ ³ | █ ³ | █ ³ | █ ³ |
| Cost of avelumab | | | | | | |
| Total avelumab prescriptions | █ ¹ | █ ¹ | █ ² | █ ² | █ ² | █ ² |
| PBS/RPBS cost (\$2,715.71 per script) | \$█ ⁵ | \$█ ⁶ | \$█ ⁶ | \$█ ⁷ | \$█ ⁷ | \$█ ⁷ |
| Patient co-payment (\$17.38 per original script) | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ |
| Net PBS/RPBS cost of avelumab | \$█ ⁵ | \$█ ⁶ | \$█ ⁶ | \$█ ⁷ | \$█ ⁷ | \$█ ⁷ |
| Cost to PBS/RPBS inclusive financial stopping rule | \$█ ⁵ | \$█ ⁶ | \$█ ⁶ | \$█ ⁷ | \$█ ⁷ | \$█ ⁷ |
| Change in cost of pembrolizumab | | | | | | |
| Change in pembrolizumab scripts | -█ ⁴ | -█ ⁴ | -█ ⁴ | -█ ⁴ | -█ ⁴ | -█ ⁴ |
| PBS/RPBS cost (\$7,823.81 per script) ¹ | -\$█ ⁴ | -\$█ ⁵ | -\$█ ³ | -\$█ ⁶ | -\$█ ⁶ | -\$█ ⁶ |
| Patient copayments (\$17.38 per original script) | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ |
| Total cost displaced pembrolizumab | -\$█ ⁵ | -\$█ ⁶ | -\$█ ⁴ | -\$█ ⁶ | -\$█ ⁶ | -\$█ ⁶ |
| Change in cost of paclitaxel | | | | | | |
| Change in paclitaxel scripts | █ ³ | █ ³ | █ ³ | █ ⁴ | █ ⁴ | █ ⁴ |
| PBS/RPBS cost (\$171.70 per script) | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ |
| Patient copayments (\$17.38 per original script) | -\$█ ⁸ | -\$█ ⁸ | -\$█ ⁸ | -\$█ ⁸ | -\$█ ⁸ | -\$█ ⁸ |
| Total cost displaced pembrolizumab | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ |
| Change in cost of docetaxel | | | | | | |
| Change in docetaxel scripts | █ ³ | █ ³ | █ ³ | █ ³ | █ ³ | █ ³ |
| PBS/RPBS cost (\$165.24 per script) | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ |
| Patient copayments (\$17.38 per original script) | -\$█ ⁸ | -\$█ ⁸ | -\$█ ⁸ | -\$█ ⁸ | -\$█ ⁸ | -\$█ ⁸ |
| Total cost displaced docetaxel | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ |
| Net cost to the PBS/RPBS | | | | | | |
| Net cost to PBS/RPBS of avelumab | \$█ ⁵ | \$█ ⁶ | \$█ ⁶ | \$█ ⁷ | \$█ ⁷ | \$█ ⁷ |
| Cost offsets for subsequent anticancer treatments | -\$█ ⁵ | -\$█ ⁵ | -\$█ ³ | -\$█ ⁵ | -\$█ ⁶ | -\$█ ⁶ |
| Overall net cost to PBS/RPBS (exclusive of financial stopping rule rebate) | -\$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁵ | \$█ ⁵ | \$█ ⁵ |
| Cost to PBS/RPBS (inclusive of financial stopping rule rebate) | -\$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁵ | \$█ ⁵ | \$█ ⁵ |
| Net cost the MBS | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁸ |
| Net cost to Government | -\$█ ⁸ | \$█ ⁸ | \$█ ⁸ | \$█ ⁵ | \$█ ⁵ | \$█ ⁵ |

Source: Table 4.3-1, p206; Table 4.3-2, p207; Table 4.3-4, p208; Table 4.3-5, p209; Table 4.3-7, p210; Table 4.5-3, p212 of the submission; 'Bavencio (avelumab) Utilisation and Cost' Excel workbook.

Public Summary Document– March 2021 PBAC Meeting

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

² 10,000 to < 20,000

³ < 500

⁴ 500 to < 5,000

⁵ \$10 million to < \$20 million

⁶ \$20 million to < \$30 million

⁷ \$30 million to < \$40 million

⁸ \$0 to < \$10 million

- 6.66 The listing of avelumab was estimated to result in a cost saving to the PBS/RPBS in Year 1 of listing, increasing to a cost of \$10 to < \$20 million in Year 6, a total of \$40 to < \$50 million over the first six years of listing. The PBAC noted these costs were based on the published price of pembrolizumab and that incorporation of the effective price of this medicine will impact on the estimated net cost to the PBS.
- 6.67 The DUSC considered the financial estimates to be uncertain and likely to be overestimated. The main issues included:
- While the epidemiological approach employed to derive the eligible population appeared reasonable overall, it was relatively complex and relied upon multiple international estimates, some of which had unclear applicability to the Australian setting.
 - The submission estimated that 90% of patients are treated with first line platinum based chemotherapy which DUSC considered was an overestimate. DUSC considered a reasonable estimate would be that 70% of patients are treated with first-line platinum based chemotherapy given the renal impairment, age and comorbidities in this population.
 - Uncertainty regarding the uptake of avelumab. DUSC considered that there is likely to be a population of patients who would prefer a 'treatment holiday' after undergoing rigorous platinum therapy. This population would likely then prefer waiting two months and opting for pembrolizumab as second-line therapy with a three-weekly dosing schedule. DUSC considered that the uptake rate of 65% in year one is likely to be underestimated and the plateau of 95% by year three is likely overestimated.
 - The duration of avelumab treatment was based on data derived from the economic model. The model-based treatment duration estimates incorporated uncertainty associated with the economic model, including the extrapolation of the time to treatment discontinuation curve, and the use of avelumab beyond disease progression. DUSC noted that the median treatment duration for melanoma patients using nivolumab or pembrolizumab first line was 8.3 months and 6.8 months respectively. DUSC noted that the response rate to immune checkpoint inhibitors in melanomas is higher than in urothelial carcinomas and the proposed treatment duration for newly initiating patients of approximately 14.8 months (6 year restricted mean) is unlikely. The pre-PBAC response argued that the comparison of melanoma and urothelial cancer was not relevant as the two conditions do not share any relevant characteristics.

- 6.68 The submission estimated that < 500 patients are likely to be eligible for treatment through the grandfather restriction. The pre-PBAC response noted that given the TGA registration was expedited, it was likely that the number of grandfathered patients will exceed the < 500 patients accounted for in the financial estimates.

Quality Use of Medicines

- 6.69 No quality use of medicines issues were identified in the submission, and no activities to support the quality use of medicines were proposed. DUSC noted that a flat dosing of 800 mg every two weeks was proposed. DUSC considered it was unclear whether this dosing schedule was applicable to patients with a higher body weight.

Financial Management – Risk Sharing Arrangements

- 6.70 The submission proposed a financial stopping rule where the cost of avelumab incurred after the fourth year of treatment would be provided as a rebate to government. The DUSC and ESC considered the proposal of a four year treatment duration was inappropriate given urothelial cancer is an aggressive disease and it would be unlikely that patients would use avelumab for this long. The PBAC further noted that this only impacted on the financial estimated from year 5 onwards, and hence the impact, if any, would unlikely to be observed during the period covered by a RSA.
- 6.71 In the July 2018 consideration of pembrolizumab, the PBAC considered that a risk sharing arrangement was required to address potential use outside the proposed restriction and the uncertain treatment duration (paragraph 6.43, pembrolizumab public summary document, July 2018 PBAC meeting). The PSCR proposed that any other risks in the use of avelumab for locally advanced or metastatic urothelial carcinoma that may result in additional costs to the PBS could be managed with a risk sharing arrangement.
- 6.72 The PBAC noted that the current listing of pembrolizumab for locally advanced or metastatic urothelial cancer allows use in patients who have progressed on or after prior platinum based chemotherapy. The submission stated that the view of 11 Australian oncologists experienced in the treatment of patients with locally advanced or metastatic urothelial carcinoma was that 75% of patients do not progress after 4 to 6 cycles of platinum-based chemotherapy. This is in between the weighted average of approximately 78% at 16 weeks and 58% at 28 weeks estimated from the published literature. As such, the PBAC considered it likely that 25% of patients do progress on platinum-based chemotherapy and hence would not be eligible for treatment with avelumab. The PBAC noted that, assuming they remain fit enough for second line treatment, these patients would receive pembrolizumab in sequence without a treatment break. In addition, the PBAC noted the DUSC advice that some patients may prefer a ‘treatment holiday’ after undergoing rigorous platinum therapy and hence may choose pembrolizumab on progression over avelumab maintenance therapy.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of avelumab, for the maintenance treatment of locally advanced (Stage III) or metastatic (Stage IV) urothelial carcinoma in patients whose disease has not progressed following first-line platinum-based chemotherapy, on the basis that it should be available only under special arrangements under Section 100 – Efficient Funding of Chemotherapy.
- 7.2 The PBAC was satisfied that avelumab provides for some patients, a significant improvement in overall survival over best supportive care (BSC). The PBAC considered that, while the magnitude of the incremental benefit of the use of maintenance avelumab + BSC versus BSC + initiation of pembrolizumab on disease progression was uncertain, it was likely avelumab in this context would offer benefit to some patients. The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of avelumab could be brought into an acceptable range with a price reduction along with a Risk Sharing Arrangement (RSA) to reduce any residual uncertainties with the financial estimates.
- 7.3 The PBAC noted the consumer comments from BEAT Bladder Cancer Australia and Rare Cancers Australia which highlighted the negative impact on quality of life associated with this condition. In addition, the PBAC noted the Medical Oncology Group of Australia’s strong support for the submission.
- 7.4 The PBAC noted the submission’s nominated comparator of BSC. However, the PBAC considered that BSC followed by subsequent therapy with pembrolizumab on progression for patients who respond to first-line platinum-based chemotherapy was an appropriate comparator as this would reflect Australian clinical practice.
- 7.5 The PBAC noted that overall survival in the JAVELIN Bladder 100 trial was statistically significantly longer in the avelumab + BSC arm compared to the BSC arm (median overall survival 21.4 months and 14.3 months respectively; hazard ratio = 0.69 [95% CI: 0.56, 0.86]). The PBAC considered that, although statistically significant, the benefit evident for progression-free survival (PFS) was small with independent review committee-assessed median PFS reported as 3.7 months for avelumab + BSC versus 2.0 months for BSC (Hazard ratio = 0.62 [95% CI: 0.52, 0.75]). The PBAC considered that, although the overall survival data presented supported the claim of superior comparative effectiveness versus BSC, the small median PFS benefit reported highlighted the importance of subsequent anticancer therapies.
- 7.6 The PBAC noted that pembrolizumab is PBS-listed for the treatment of urothelial carcinoma in patients who have experienced disease progression following treatment with platinum-based chemotherapy. As such, the PBAC considered BSC + subsequent pembrolizumab reflects current Australian clinical practice (see paragraph 7.4). The PBAC noted that in the BSC arm of JAVELIN Bladder 100, 43.7% (153/350) of patients received subsequent treatment with a PD-1/PD-L1 inhibitor. This equates to 61% (153/251) of patients who experienced disease progression in the BSC arm. The PBAC

agreed with the Pre-Sub-Committee Response (PSCR) that in Australian clinical practice a greater proportion of patients (80%) treated with BSC alone receive second-line treatment with a PD-1/PD-L1 inhibitor than that observed in the JAVELIN Bladder 100 trial. The PBAC considered the overall survival results in the key trial were impacted by differences in the pattern of use of subsequent anticancer therapies between treatment arms, with the results likely to have favoured avelumab. Despite this the PBAC considered it reasonable to anticipate that maintenance avelumab would offer benefit to some patients versus waiting for disease progression to initiate second-line pembrolizumab, although the magnitude of the incremental benefit is uncertain.

- 7.7 The PBAC agreed with the ESC that the benefit of avelumab on overall survival in PD-L1 negative patients was uncertain (see paragraphs 6.30 and 6.39). The PBAC noted the JAVELIN Bladder 100 trial was not powered to show a statistical response in the PD-L1 negative subgroup analysis, however, like the KEYNOTE-045 study of pembrolizumab, a numerical advantage was seen in PD-L1 negative patients but the difference was not statistically significant. The PBAC considered that there was insufficient evidence of clinically important treatment effect modification by PD-L1 expression to justify restricting avelumab to a specific subgroup defined using this variable. The PBAC noted this was consistent with the current second-line listing of pembrolizumab for this condition.
- 7.8 The PBAC considered the claim of inferior safety compared to BSC to be reasonable. The PBAC advised that avelumab would be expected to have a similar safety profile to second-line pembrolizumab with known and manageable adverse events.
- 7.9 The PBAC noted the submission presented a cost-utility analysis to estimate the cost-effectiveness of avelumab with a base case incremental cost-effectiveness ratio (ICER) of \$55,000 to < \$75,000/QALY. The PBAC noted a difference in the proportion patients with disease progression in the BSC arm who would commence a subsequent PD-1/PD-L1 inhibitor between the model (80%) and the JAVELIN Bladder 100 trial (61%). The PBAC agreed with the ESC that as a result there were higher costs associated with PD-1/PD-L1 inhibitor therapy in the BSC arm of the model without corresponding adjustments to efficacy outcomes which favoured avelumab.
- 7.10 The PBAC agreed with ESC that a 7.5 year time horizon was more appropriate than the 10 year time horizon used in the base case, increasing the ICER from \$55,000 to < \$75,000/QALY to \$55,000 to < \$75,000/QALY when applied. In addition, the PBAC agreed with the DUSC and ESC that the proposed financial stopping rule was inappropriate given urothelial cancer is an aggressive disease and hence its impact was likely to be minimal, especially over the time frame of a RSA. The PBAC noted that the ICER increased to \$95,000 to < \$115,000/QALY when the financial stopping rule was removed, with the large increase in the ICER reflecting that a small proportion of patients were modelled to continued treatment for a long duration (with 3% still on treatment at 10 years). The PBAC noted that the BSC costs differed to those presented in Table 14 when the effective price of pembrolizumab was applied. Overall, the PBAC

considered that an ICER of \$55,000 to < \$75,000/QALY was high but accepted it in this circumstance. However, the PBAC considered that the base case ICER was underestimated due to reliance on optimistic assumptions and inputs in the economic model. The PBAC considered that appropriate model inputs should include:

- a 7.5-year time horizon;
- use of the exponential function to extrapolate time to treatment discontinuation for the avelumab + BSC arm (mean treatment 12.64 months);
- no financial stopping rule; and
- the effective price of pembrolizumab.

The PBAC advised that with the above respecified model inputs, a price reduction would be required to achieve the cost-effective ICER of \$55,000 to < \$75,000/QALY.

- 7.11 The PBAC noted DUSC considered the financial estimates to be overestimated with the key areas of uncertainty the proportion of patients receiving first line platinum based chemotherapy, the uptake of avelumab and the duration of treatment. The PBAC agreed with DUSC that the proposed avelumab duration of treatment was likely overestimated. The PBAC considered that a revised mean duration of avelumab treatment of 12.64 months, based on the respecified model inputs (see paragraph 7.10), was appropriate. The PBAC considered the proportion of patients treated with first line platinum based chemotherapy (90%) and the uptake rates as proposed in the submission to be uncertain and to reflect the upper end of the range of likely use. Acknowledging these uncertainties, the PBAC considered the financial estimates presented in the submission represent the likely maximum cost. The PBAC noted that the financial estimates would need to be recalculated to take into account the outcome of its considerations regarding the revised mean treatment duration and the avelumab price reduction required to achieve cost-effectiveness (see paragraph 7.10).
- 7.12 The PBAC did not consider it was appropriate to include the additional < 500 patients for the purposes of estimating a grandfathered population in year 1 of listing. Based on the information provided by the sponsor it was not clear that these patients were not already captured in the uptake proposed within the financial estimates. It was also apparent from the information provided by the sponsor that the early access program had not yet commenced at the time of PBAC consideration, and so the PBAC considered it was reasonable to conclude that these patients should be captured within the existing patient pool.
- 7.13 The PBAC recommended that avelumab be included within the current RSA for second-line pembrolizumab to address any residual uncertainty regarding the uptake rate and the costs associated with the different treatment durations of these two therapies. The PBAC considered that the current financial caps should be revised to take into account: (i) the assumption that 25% of patients currently covered by the caps will not be eligible to receive avelumab as they will have progressed on platinum-based chemotherapy (see paragraph 6.72), (ii) the avelumab uptake as presented in

the submission, (iii) the difference in the treatment duration and the cost per administration for avelumab versus pembrolizumab, taking into account the impact of paragraph 7.10. The PBAC considered an increase in the patient numbers informing the current financial caps was not required as this was adequately accounted for with the assumed uptake rate for second-line pembrolizumab.

7.14 The PBAC noted the following flow-on restriction changes to the current listing for pembrolizumab for locally advanced (Stage III) or metastatic (Stage IV) urothelial carcinoma [11632F, 11646Y]:

- Addition of clinical criterion to initial treatment restriction ‘Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition’;
- Removal of the clinical criterion in the continuing treatment restriction stating ‘Patient must have stable or responding disease’ and addition of clinical criterion ‘Patient must not have developed disease progression while being treated with this drug for this condition.’

7.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for avelumab:

- a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over BSC with subsequent pembrolizumab as the magnitude of the incremental benefit is uncertain;
- b) The treatment is not expected to address a high and urgent unmet clinical need because other subsidised therapies are available;
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing/recommended listing:

| Name, Restriction, Manner of administration and form | PBS item code | Max. Amount | No. of Rpts | Manufacturer |
|---|-------------------------------|----------------|----------------|--------------------------|
| AVELUMAB, 200 mg/10 mL injection, 10 mL vial | NEW (Public) NEW (Private) | 800 mg | 7 | Merck Healthcare Pty Ltd |
| Available brands | | | | |
| Bavencio (avelumab 200 mg/10 mL injection, 10 mL vial) | | | | |

Initial treatment Restriction Summary [NEW] / Treatment of Concept (ToC): [NEW]

| | |
|-------------------------------|--|
| Category / Program: | Section 100 – Efficient Funding of Chemotherapy |
| Prescriber type: | Medical Practitioners |
| Severity: | Locally advanced (Stage III) or metastatic (Stage IV) |
| Condition: | Urothelial cancer |
| PBS Indication: | Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer [21171] |
| Treatment phase: | Maintenance therapy - Initial treatment |
| Restriction Level: | <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (Telephone/electronic) |
| Clinical criteria: | |
| | Patient must have received first-line platinum-based chemotherapy, |
| | AND |
| Clinical criteria: | |
| | Patient must not have progressive disease following first-line platinum-based chemotherapy |
| | AND |
| Clinical criteria: | |
| | Patient must have a WHO performance status of 0 or 1, |
| | AND |
| Clinical criteria: | |
| | The treatment must be the sole PBS-subsidised therapy for this condition |
| Administrative advice: | |
| | In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. |
| Administrative advice: | |
| | No increase in the maximum quantity or number of units may be authorised. |
| Administrative advice: | |
| | No increase in the maximum number of repeats may be authorised. |
| Administrative advice: | |
| | Special Pricing Arrangements apply |

| Name, Restriction, Manner of administration and form | PBS item code | Max. Amount | No. of Rpts | Manufacturer |
|---|-------------------------------|----------------|----------------|--------------------------|
| AVELUMAB, 200 mg/10 mL injection, 10 mL vial | NEW (Public) NEW (Private) | 800 mg | 11 | Merck Healthcare Pty Ltd |
| Available brands | | | | |
| Bavencio (avelumab 200 mg/10 mL injection, 10 mL vial) | | | | |

Public Summary Document– March 2021 PBAC Meeting

Continuing treatment Restriction Summary [NEW] / Treatment of Concept (ToC): [NEW]

| | |
|-------------------------------|--|
| Category / Program: | Section 100 – Efficient Funding of Chemotherapy |
| Prescriber type: | Medical Practitioners |
| Severity: | Locally advanced (Stage III) or metastatic (Stage IV) |
| Condition: | Urothelial cancer |
| PBS Indication: | Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer [21171] |
| Treatment phase: | Maintenance therapy – Continuing treatment |
| Restriction Level: | <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (Telephone/electronic) |
| Clinical criteria: | |
| | Patient must have previously received PBS-subsidised treatment with this drug for this condition, |
| | AND |
| Clinical criteria: | |
| | Patient must not have developed disease progression while being treated with this drug for this condition, |
| | AND |
| Clinical criteria: | |
| | The treatment must be the sole PBS-subsidised therapy for this condition, |
| | AND |
| Administrative advice: | No increase in the maximum quantity or number of units may be authorised. |
| Administrative advice: | No increase in the maximum number of repeats may be authorised. |
| Administrative advice: | Special Pricing Arrangements apply |

| Name, Restriction, Manner of administration and form | PBS item code | Max. Amount | No. of Rpts | Manufacturer |
|---|-------------------------------|-------------|-------------|--------------------------|
| AVELUMAB, 200 mg/10 mL injection, 10 mL vial | NEW (Public) NEW (Private) | 800 mg | 7 | Merck Healthcare Pty Ltd |
| Available brands | | | | |
| Bavencio (avelumab 200 mg/10 mL injection, 10 mL vial) | | | | |

Grandfathering treatment Restriction Summary [NEW] / Treatment of Concept (ToC): [NEW]

| | |
|----------------------------|--|
| Category / Program: | Section 100 – Efficient Funding of Chemotherapy |
| Prescriber type: | Medical Practitioners |
| Severity: | Locally advanced (Stage III) or metastatic (Stage IV) |
| Condition: | Urothelial cancer |
| PBS Indication: | Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer |
| Treatment phase: | Maintenance therapy – Grandfathering treatment |
| Restriction Level: | <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (Telephone/electronic) |
| Clinical criteria: | |
| | Patient must have received non-PBS-subsidised treatment with this drug for this indication prior to [date of PBS listing], |
| | AND |
| Clinical criteria: | |
| | Patient must have received first-line platinum-based chemotherapy prior to initiation of non-PBS-subsidised treatment with this drug for this condition, |
| | AND |
| Clinical criteria: | |
| | Patient must not have progressive disease following first-line platinum-based chemotherapy |
| | AND |
| Clinical criteria: | |
| | Patient must have had a WHO performance status of 0 or 1 prior to initiation of non-PBS-subsidised treatment with this drug for this condition, |
| | AND |

Public Summary Document– March 2021 PBAC Meeting

| | |
|--|---|
| | Clinical criteria: |
| | Patient must not have developed disease progression while being treated with this drug for this condition, |
| | AND |
| | Clinical criteria: |
| | The treatment must be the sole PBS-subsidised therapy for this condition, |
| | Administrative advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. |
| | Administrative advice: No increase in the maximum quantity or number of units may be authorised. |
| | Administrative advice: No increase in the maximum number of repeats may be authorised. |
| | Administrative advice: Special Pricing Arrangements apply |

8.2 Flow-on changes to existing listing for pembrolizumab in indication are as follows:

Add the following to Initial treatment restriction:

Restriction Summary 9896 / ToC: 9921: Authority Required: Streamlined

| | |
|--|--|
| | Clinical criteria: |
| | <i>Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition</i> |

Make the following changes to the Continuing treatment:

Restriction Summary 9967 / ToC: 9894: Authority Required: Streamlined

| | |
|--|--|
| | Clinical criteria: |
| | Patient must have stable or responding disease |
| | Clinical criteria: |
| | <i>Patient must not have developed disease progression while being treated with this drug for this condition</i> |

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 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.

10 Sponsor's Comment

Merck Healthcare welcomes the PBAC's decision to recommend avelumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma, an aggressive cancer with high clinical need for additional treatment options.