

5.01 AVELUMAB,

Solution concentrate for I.V. infusion 200 mg in 10 mL,

Bavencio[®],

Merck Serono Australia Pty Ltd

1 Purpose of Application

- 1.1 Authority required (Streamlined) listing for avelumab for the treatment of second-line metastatic Merkel cell carcinoma (mMCC) in patients that have progressed following chemotherapy. Avelumab has not been previously considered by the PBAC for any indication.
- 1.2 The basis for the requested listing was a cost-utility analysis compared to Australian standard of care chemotherapy regimens (cyclophosphamide + doxorubicin + vincristine, cisplatin + etoposide, or carboplatin + etoposide).

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

Component	Description
Population	Patients with metastatic Merkel Cell Carcinoma (mMCC)
Intervention	Avelumab 10 mg/kg body weight administered intravenously over 60 minutes once every 2 weeks
Comparator	A range of chemotherapy (CTX) regimens
Outcomes	ORR, complete response rate, duration of response, PFS and OS.
Clinical claim	The therapeutic claim presented is that: Avelumab in 2L+ mMCC is superior in terms of effectiveness compared to chemotherapy. Avelumab in 2L+ mMCC is noninferior in terms of safety compared to chemotherapy. The therapeutic claim would also apply to 1L mMCC with evolving data suggesting that avelumab is even more effective earlier in the treatment pathway with higher response rates and durability.

mMCC: metastatic Merkel Cell Carcinoma; CTX: chemotherapy; 2L+: second-line therapy; ORR: overall response rate; PFS: progression free survival; OS: overall survival; 1L: first line therapy; CR: complete response.

Source: Table 1.1.1, p12 of the submission and added during the evaluation.

2 Requested listing

- 2.1 The proposed PBS listing and proposed restriction criteria for avelumab in second line treatment of mMCC are summarised in the tables below.

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

Summary of proposed PBS listing

Name, Restriction, Manner of administration and form	Max. Amount (units)	No. of Rpts	DPMA	Proprietary name	Manufacturer
Avolumab, 200 mg injection: liquid, 1 vial avelumab 200 mg/10 mL injection, 10 mL vial	6	8	Public: \$8,227.99 (published) \$ [REDACTED] (effective) Private \$8,380.58 (published) \$ [REDACTED] (effective)	Bavencio® SG	Merck Serono Australia Pty Ltd
Category / Program:	Section 100 – Efficient funding of chemotherapy				
Prescriber type:	Medical Practitioners				
Episodicity:	-				
Severity:	Stage IV (metastatic)				
Condition:	Merkel Cell Carcinoma				
PBS Indication:	Stage IV (metastatic) Merkel Cell Carcinoma				
Treatment phase:	Treatment phase: Initial treatment				
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined				
Treatment criteria:	-				
Clinical criteria:	<p>The condition must have progressed following treatment with chemotherapy unless contraindicated or not tolerated according to the TGA approved Product Information.</p> <p><i>The condition must have progressed following treatment with chemotherapy;</i> OR <i>Patient must have a contraindication or intolerance to treatment with chemotherapy;</i> AND The treatment must be the sole PBS-subsidised therapy for this condition; AND The treatment must not exceed a total of 9 doses at a maximum dose of 10 mg/ per kg every 2 weeks AND <i>Patient must have WHO performance status score of 1 or less.</i></p>				
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.				
Administrative advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.				

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Name, Restriction, Manner of administration and form	Max. Amount (units)	No. of Rpts	DPMA	Proprietary name	Manufacturer
Avolumab, 200 mg injection: liquid, 1 vial avelumab 200 mg/10 mL injection, 10 mL vial	6	11	Public: \$8,227.99 (published) \$ [REDACTED] (effective) Private \$8380.58 (published) \$ [REDACTED] (effective)	Bavencio® SG	Merck Serono Australia Pty Ltd
Category / Program:	Section 100 – Efficient funding of chemotherapy				
Prescriber type:	Medical Practitioners				
Episodicity:	-				
Severity:	Stage IV (metastatic)				
Condition:	Merkel Cell Carcinoma				
PBS Indication:	Stage IV (metastatic) Merkel Cell Carcinoma				
Treatment phase:	Continuing treatment 4 – from initial treatment				
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined				
Treatment criteria:	-				
Clinical criteria:	<p>The treatment must be the sole PBS-subsidised therapy for this condition; AND Patient must have previously been issued with an authority prescription for this drug for this condition; AND Patient must have stable or responding disease <i>according to the Response Evaluation Criteria In Solid Tumours (RECIST)</i>; AND The treatment must not exceed a maximum dose of 10 mg per kg every 2 weeks.</p>				
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.				
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised. <i>Special Pricing Arrangements apply.</i></p> <p><i>Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions. Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) is small changes that do not meet above criteria.</i></p>				

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Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	DPMA	Proprietary name	Manufacturer
Avelumab, 200 mg injection, liquid, 1 vial avelumab 200 mg/10 mL injection, 10 mL vial	6	11	Public: \$8,227.99 (published) \$ [REDACTED] (effective) Private \$8380.58 (published) \$ [REDACTED] (effective)	Bavencio® SG	Merck Serono Australia Pty Ltd
Category / Program:	Section 100 – Efficient funding of chemotherapy				
Prescriber type:	Medical Practitioners				
Episodicity:	-				
Severity:	Stage IV (metastatic)				
Condition:	Merkel Cell Carcinoma				
PBS Indication:	Stage IV (metastatic) Merkel Cell Carcinoma				
Treatment phase:	Treatment phase: Grandfathering				
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined				
Treatment criteria:	-				
Clinical criteria:	<p>The treatment must be the sole PBS-subsidised therapy for this condition; AND Patient must have received treatment with avelumab for this condition prior to [date to be determined] AND Patient must have stable or responding disease <i>according to the Response Evaluation Criteria In Solid Tumours (RECIST)</i>; AND The treatment must not exceed a maximum dose of 10 mg per kg every 2 weeks. AND <i>Patient must have WHO performance status score of 1 or less.</i></p>				
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.				
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised. <i>Special Pricing Arrangements apply.</i></p> <p><i>Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows:</i> <i>Complete response (CR) is disappearance of all target lesions.</i> <i>Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.</i> <i>Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.</i> <i>Stable disease (SD) is small changes that do not meet above criteria.</i></p>				

- 2.2 Although the proposed listing above is for use in a second line setting following chemotherapy, the submission requested that the PBAC also consider a broader listing which would also allow use in the first-line setting. The ESC considered that given the immature evidence available for avelumab, a second-line listing may be more appropriate. However, the ESC also expressed concern that if recommended for second-line only, there may be a risk of leakage in the first line setting. The Pre-Sub-Committee-Response (PSCR) acknowledged that the data in first-line is emerging, however it noted that, in 12 countries for which reimbursement has been recommended, it has been for both the first and second line settings. The PBAC considered that although there was limited data for avelumab in the first line setting clinician preference would likely be for use in the first line setting given the low efficacy and high toxicity in using chemotherapy to treat mMCC. Overall, the PBAC considered a listing enabling use in both the first and second line settings would provide equitable access to all patients with this rare cancer.
- 2.3 The requested PBS restriction did not restrict avelumab to patients with an ECOG score of 0 or 1. The JAVELIN Merkel 200 study excluded patients with an ECOG score greater than 1. The ESC considered that it would be reasonable to restrict the ECOG performance status to 1 to align with the JAVELIN study. The PBAC considered that it may be impractical to restrict therapy to an ECOG status of 1 or less in clinical practice given the lack of treatment options and recommended that the listing not be restricted based on WHO or ECOG status.
- 2.4 The proposed PBS listing does not allow treatment beyond progression, however, treatment beyond confirmed disease progression was permitted in the JAVELIN Merkel 200 study. The PSCR stated that in the study only a small proportion of patients continued treatment beyond progression. Of the 29 patients who responded, 10 had progressed at 24 months of follow up; of these only 2 are known to have been treated beyond progression (PSCR). Conversely, 17/29 patients had ceased treatment prior to progression. Additionally, the PSCR argued that these data are consistent with feedback from clinicians (from a survey of 10 clinicians conducted by the sponsor – PSCR) who noted that treatment beyond progression would only occur in a small percentage of patients where clinical deterioration had not been observed and for a limited number of cycles so that pseudoprogression could be ruled out, although the submission stated that there is no evidence of tumour flare (pseudoprogression) with avelumab (p33 of the submission). Seven clinicians estimated that 10-30% of patients who had progressed would continue to be treated. The ESC considered that it was difficult to determine the treatment duration (see further discussion in the economic analysis section). The clinician at the sponsor hearing noted that pseudoprogression is rare, occurring in 1-2% of cases. The pre-PBAC response reiterated that the number of patients who would be treated beyond progression is uncertain, but likely to be small (approximately 10% based on the results of the clinician survey). The sponsor further argued that a maximum duration of treatment is not specified for immunotherapy drugs in the

treatment of melanoma and that the restriction wording combined with a risk sharing arrangement (RSA) will manage the financial risk to the Commonwealth.

- 2.5 The ESC noted that the submission did not propose to restrict avelumab to any subgroup of the mMCC population. Due to the mechanism of action of avelumab where it inhibits programmed death-ligand 1, PD-L1, it may be expected that avelumab would be more efficacious in patients whose tumours express a higher proportion of PD-L1. Baseline PD-L1 tumour expression status was collected during the JAVELIN Merkel 200 study for the purposes of an exploratory analysis. The submission presented subgroup analyses from the JAVELIN Merkel 200 study, which suggested a possible higher ORR in patients with PD-L1 positive tumours (1% threshold by immunohistochemistry, 36.2% vs 18.8% for PD-L1–negative tumours; 5% threshold by immunohistochemistry, 57.9% vs 23.6% for PD-L1–negative tumours) (p79 of the submission). However, it stated that durable responses occurred irrespective of baseline factors, including tumour PD-L1 status (p80 of the submission). Furthermore the TGA, in its consideration of avelumab, noted that in a condition with no established therapies and a life expectancy of less than 6 months, the level of efficacy observed in PD-L1-negative tumours is clinically meaningful (TGA clinical evaluation, p45). The ESC agreed that a meaningful response was observed in patients with both PD-L1 positive and PD-L1 negative tumours.
- 2.6 PD-L1 expression status was not collected in the retrospective observational cohort studies (Study Obs001 and Iyer 2016). It is unlikely that this information would have been available given there were no treatment anti PD-1/PD-L1 treatment options at the time patients in these observational studies were diagnosed and received treatment. The collection of tumour PD-L1 status in Study Obs001 would have provided greater insight as to whether tumour PD-L1 status is a prognostic marker for PFS and OS as opposed to modifying efficacy in patients treated with avelumab. The PBAC considered that the exclusion of PD-L1 as an eligibility biomarker for this medicine in mMCC is appropriate. Both the ESC and the PBAC noted that there are currently phase II clinical trials for related immune checkpoint inhibitors pembrolizumab and nivolumab for the treatment of MCC.

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

3 Background

Registration status

- 3.1 TGA status: avelumab was TGA registered on 03 January 2018 for the treatment of adults and paediatric patients 12 years and older with mMCC.

Previous PBAC consideration

- 3.2 Avelumab has not previously been considered by the PBAC for this indication.

4 Population and disease

- 4.1 Merkel Cell Carcinoma (MCC) is a rare, aggressive skin cancer associated with poor prognosis. Currently there is a significant unmet need for patients with metastatic disease.
- 4.2 The proposed clinical management algorithm suggested that avelumab be used as a second-line and later line treatment option after patients have progressed using chemotherapy.
- 4.3 As noted above, the submission requested that the PBAC consider a “line agnostic PBS listing” (p24 of the submission).

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

5 Comparator

- 5.1 The submission nominated current Australian standard of care as the main comparator, specifically one of three chemotherapy regimens: cyclophosphamide + doxorubicin + vincristine, carboplatin + etoposide, or cisplatin + etoposide (p17-18 of the submission).
- 5.2 The chemotherapy regimens were weighted in the economic model. The weights were informed by an Australian clinician survey.
- 5.3 The PBAC considered the main comparators nominated by the submission were reasonable. However, the Australian clinician survey, which informed each of the comparators and their weighting, had a poor response rate (16.5%) and the specialties of the clinicians were not specified.

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 highlighted that mMCC is a rare but aggressive cancer, and noted that chemotherapy is not a very effective therapy for this patient group, as patients are unable to tolerate effective doses and the duration of effect is short. Additionally, the clinician noted that as MCC generally occurs in older patients, it is difficult to administer chemotherapy, particularly multiple chemotherapy treatments, because of general frailty and comorbid diseases. On this basis the clinician stated a preference for the listing to allow use in the first line setting. Emerging evidence from the June 2018 American Society of Clinical Oncology (ASCO) Annual Meeting was presented to the PBAC which highlighted that avelumab demonstrated durable responses that are not seen with

chemotherapy¹. Data from the sponsor's global access program were also presented and the overall response rate (ORR) was 51.6%, including complete response in 24.8% (n=39) of patients and partial response in 26.8% (n=42) of patients. In addition, no new safety signals were identified.² When asked by the PBAC about duration of treatment, the clinician confirmed that in clinical practice, response to avelumab could be observed within 6-8 weeks of commencing treatment and there was a deepening of response over 1-1.5 years. The clinician stated that in the maintenance setting, the ideal approach would be to treat beyond 1 year up to about 2 years, but this was hard to determine as there is currently no data available to confirm this approach. The clinician also noted that pseudoprogression is only seen in a small number (1-2%) of cases; and confirmatory scans for progression could be performed 6 – 8 weeks after initially identifying possible progression. The clinician noted that approximately 50% of patients in clinical practice had an ECOG performance status of ≥ 1 , where patients with an ECOG performance status of 3 were not likely to be treated with avelumab. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (3), health care professionals (3) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from the health professionals described that conventional treatments are not effective in treating mMCC and phase II data demonstrate that avelumab is not only effective but also has lasting benefits, at or beyond, 1-2 years after starting therapy. The comments noted that the benefits observed are comparable to those with PD-1 inhibitors such as nivolumab and pembrolizumab. The comments also stated that there is currently a real unmet need in the treatment of this rare cancer and therefore a first line listing is preferred. Comments from individuals noted that treatment with avelumab was associated with side effects although it was more tolerable than chemotherapy. Additionally, it was noted that there are significant out of pocket costs for patients with rare cancers and having avelumab available on the PBS would help with the financial burden.
- 6.3 The PBAC noted the advice received from the Australia and New Zealand Melanoma Trials Group (ANZMTG), Rare Cancers Australia and The Unicorn Foundation supporting the evidence presented in the submission for avelumab. Advice from ANZMTG stated that the data support that avelumab should be standard of care

¹ Nghiem et al. ASCO ASM 2018, Two-year efficacy and safety update from JAVELIN Merkel 200 part A: A registrational study of avelumab in metastatic Merkel cell carcinoma progressed on chemotherapy, abstract 9507.

² Walker et al. ASCO ASM 2018, Second-line avelumab treatment of patients with metastatic Merkel cell carcinoma: Experience from a global expanded access program, Abstract No. 9537

therapy for mMCC, including as first line therapy, as it is important to note that mMCC patients can deteriorate quickly after first line chemotherapy and thus miss their opportunity to receive second line avelumab. The Unicorn Foundation stated that the Scottish Medicines Consortium reported avelumab represents an active treatment option for some patients who are not fit enough to receive chemotherapy, due to its more favourable adverse effect profile. The comments also highlighted that access to PD-1 drugs for mMCC is limited in Australia and clinical trials and compassionate access programs reach very few patients. Furthermore, it was noted that generally patients with MCC are over 70 years of age and have suppressed immune systems who endure chemotherapy with the expectation of little success.

- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the avelumab submission, on the basis of significant unmet need in the treatment of mMCC. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for avelumab for first and second line treatment of mMCC, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)³.

Clinical trials

- 6.5 The submission claimed that no head-to-head trials were available.
- 6.6 The submission was based on a naïve indirect comparison of one single arm, open label study of patients treated with avelumab in first-line and second-line mMCC: JAVELIN Merkel 200 (N=162) compared to one retrospective observational cohort study of patients treated with chemotherapy: Obs001 (N=121).
- 6.7 The submission was also supported by an additional retrospective observational cohort study: Iyer 2016 (N=30).
- 6.8 The first-line cohort of the JAVELIN Merkel 200 study is still recruiting patients.
- 6.9 Details of the studies presented in the submission are provided in the table below.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Study EMR100070003 Part A (hereafter referred to as JAVELIN Merkel 200 Part A) – 2L+	EMR 100070-003 Interim CSR. A Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma (JAVELIN Merkel 200).	17 August 2016
	Addendum 1 to EMR 100070-003 CSR: 29 November 2016 (data cut-off: 3 September 2016)	29 November 2016

³ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Trial ID	Protocol title/ Publication title	Publication citation
	<p>Addendum 3 to EMR 100070-003 CSR: 16 June 2017 (data cut-off: 24 March 2017)</p> <p>Preliminary report of the interim analysis for Study EMR 100070-003 Part A (data cut-off: 26 September 2017)</p> <p>Kaufman HL et al. Avelumab in patients with CTX-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial.</p> <p>Kaufman HL et al. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after ≥1 year of followup: JAVELIN Merkel 200, a phase 2 clinical trial.</p> <p>Bharmal, M., F. Fofana, C. Dias Barbosa, et al. Sychometric validation of the FACT-M questionnaire in patients with merkel cell carcinoma.</p> <p>Bharmal, M., F. Fofana, L. Mahnke, et al. (2017). "Non-progression during avelumab treatment is associated with clinically relevant improvements in health-related quality of life in patients with Merkel cell carcinoma."</p> <p>Kaufman, H., O. Hamid, S. P. D'Angelo, et al. (2015). "A phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in patients with metastatic Merkel cell carcinoma."</p> <p>Kaufman, H., M. Hunger, L. Mahnke, et al. (2017). "Non-progression on treatment with avelumab contributes to gains in health utility scores in patients with metastatic merkel cell carcinoma."</p> <p>Kaufman, H., M. Kraemer, C. Dias Barbosa, et al. (2016). "Patient perspectives on merkel cell carcinoma (MCC) and its treatment with a novel agent (avelumab): Findings from in-depth qualitative patient interviews."</p> <p>Kaufman, H., J. Lambert, C. Dias Barbosa, et al. (2017). "Patient experiences with avelumab vs CTX for treating merkel cell carcinoma: Results from protocol specified qualitative research."</p> <p>Kaufman, H., J. S. Russell, O. Hamid, et al. (2016). "Avelumab (MSB0010718C; anti-PD-L1) in patients with metastatic Merkel cell carcinoma previously treated with CTX: Results of the phase 2 JAVELIN MERKEL 200 Merkel 200 trial."</p> <p>Kelly, K., J. R. Infante, M. H. Taylor, et al. (2017). "Safety profile of avelumab in patients with advanced solid tumors: A JAVELIN MERKEL 200 pooled analysis of phase 1 and 2 data."</p> <p>Shapiro, I., H. J. Grote, V. D'Urso, et al. (2017). "Exploratory biomarker analysis in avelumab-treated patients with metastatic Merkel cell carcinoma progressed after CTX."</p>	<p>16 June 2017</p> <p>16 January 2018</p> <p>The Lancet Oncology. 2016;17(10):1374-85.</p> <p>Journal for ImmunoTherapy of Cancer (2018) 6:7</p> <p>Value in Health 20(5): A121.</p> <p>Journal of Clinical Oncology 35(15).(Bharmal et al. 2017b)</p> <p>Journal of Clinical Oncology 33(15). (Kaufman et al. 2015)</p> <p>Value in Health 20(5): A119-A120. (Kaufman et al. 2017)</p> <p>Value in Health 19(7): A745. (Kaufman et al. 2016)</p> <p>Journal of Clinical Oncology 35(15). (Kaufman et al. 2017)</p> <p>Journal of Clinical Oncology 34. (Kaufman et al. 2016)</p> <p>Journal of Clinical Oncology 35(15). (Kelly et al. 2017)</p> <p>Journal of Clinical Oncology 35(15). (Shapiro et al. 2017)</p>
<p>Study EMR100070-003 Part B (hereafter referred to as JAVELIN Merkel 200 Part B) – 1L</p>	<p>Addendum 4 to EMR 100070-003 CSR (for Part B): 15 June 2017 (data cut-off: 24 March 2017).</p> <p>Preliminary report of the interim analysis for Study EMR 100070-003 Part B (data cut-off: 26 September 2017)</p> <p>D'Angelo, S. P., J. Russell, J. C. Hassel, et al. (2017). First-line (1L) avelumab treatment in patients (pts) with metastatic Merkel cell carcinoma (mMCC): Preliminary data from an ongoing study.</p>	<p>15 June 2017</p> <p>11 January 2018</p> <p>Journal of Clinical Oncology 35(15).</p>

Trial ID	Protocol title/ Publication title	Publication citation
Study 100070-Obs001 (hereafter referred to as Study Obs001) Part A (US) – 1L + 2L+	Observational Study Report CSR: Retrospective Observational Study to Evaluate Treatment Outcomes in Patients with Metastatic Merkel Cell Carcinoma Following CTX Cowey, C. L., Mahnke, J. Espirito, et al. (2017). Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with CTX in the USA. Cowey, C. L., L. Mahnke, J. Espirito, et al. (2017). “Real-world outcomes in patients with metastatic merkel cell carcinoma treated with first-line CTX in the united states: Results from a retrospective analysis.”	10 August 2016 Future Oncology 13(19): 1699-1710. Value in Health 20(5): A95. (Cowey et al. 2017)
Part B (Europe)– 2L+	Becker, J. C., E. Lorenz, S. Ugurel, et al. (2017). Evaluation of real-world treatment outcomes in patients with distant metastatic Merkel cell carcinoma following second-line chemotherapy in Europe.	Oncotarget 8(45): 79731-79741. (Becker et al. 2017)
(Iyer et al. 2016) – 1L +2L+	Iyer, J. G., A. Blom, R. Doumani, et al. (2016). Response rates and durability of CTX among 62 patients with metastatic Merkel cell carcinoma.	Cancer Medicine 5(9): 2294-2301.

Source: Table 2.2.1, p39-41 of the submission.

6.10 The key features of the studies are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Avelumab						
JAVELIN Merkel 200 Part A – 2L	88	OL, SA 18 months follow-up	High	Failed chemotherapy	ORR, PFS, OS	PFS, OS
JAVELIN Merkel 200 Part B – 1L	50	OL, SA 3 months follow-up	High	Treatment naïve	ORR, PFS, OS	1L was not modelled
Chemotherapy						
Study Obs001 Part A – 1L & 2L	14	RC*, OL, SA	High	Treatment naïve (1L) Failed chemotherapy (2L)	ORR, PFS, OS	PFS, OS 1L was not modelled
Study Obs001 Part B – 2L	29	RC*, OL, SA	High	Failed chemotherapy (2L)	ORR, PFS, OS	PFS, OS
Iyer 2016 – 1L & 2L	30	RC*, OL, SA	High	Treatment naïve (1L) Failed chemotherapy (2L)	ORR, PFS, OS	PFS, OS

2L: second-line; OL: open label; SA: single arm; ORR: overall response rate; PFS: progression free survival; OS: overall survival; 1L: first-line; RC: retrospective cohort; MC: multi-centre; OS: overall survival; PFS: progression-free survival; R: randomised.

*Studies were based on real world clinical practice and did not have a defined period of follow up.

Source: Compiled during the evaluation.

6.11 No patient matching across the studies was conducted in the submission. Instead it was claimed that Study Obs001 used similar inclusion and exclusion criteria as the JAVELIN Merkel 200 study and that patient characteristics were not prognostic of

outcome (p100 of the submission). However, there were differences between the inclusion/exclusion criteria and baseline characteristics of patients in each of the studies (i.e. ECOG performance status, exclusion of patients with significant co-morbidities, life expectancy of at least 12 weeks at time of recruitment).

- 6.12 Patient matching was requested during the equivalent National Institute for Health and Care Excellence (NICE) assessment in the United Kingdom, however it was noted in the evaluation that patients were not matched on enough baseline patient characteristics (e.g. ECOG status, baseline disease severity) for the groups to be sufficiently matched. The PSCR stated that matching reduced the number of patients in JAVELIN Merkel 200 from 88 to 54, and that this analysis showed increased PFS and OS for matched patients.
- 6.13 The ESC considered that overall the risk of bias across the studies is considered to be high due to a high risk of confounding caused by the studies not being randomised, differences in observed and (potentially) unobserved confounders, a lack of blinding of patients, investigators and assessors, and differences in study design and outcome assessments.
- 6.14 Furthermore, the sample sizes in the studies were low, which increases the uncertainty in the results.

Comparative effectiveness

- 6.15 The ORR, PFS and OS results from the indirect comparison are presented in Tables 4 to 6, and Figure 1.

Table 4: Response rates across the studies

	Avelumab		Study Obs001 Immunocompetent		lyer 2016 N=30
	JAVELIN Merkel 200 Part A 18 mth follow-up ITT N=88	JAVELIN Merkel 200 Part A 24 mth follow-up ITT N=88	Part A (US) N=14	Part B (EU) N=29	
BOR per RECIST 1.1, n (%)					
CR	10 (11.4)	10 (11.4)	0	0	1 (3.3)
PR	19 (21.6)	19 (21.6)	4 (28.6)	3 (10.3)	6 (20.0)
SD	9 (10.2)	NR	2 (14.3)	3 (10.3)	1 (3.3)
PD	32 (36.4)	NR	5 (35.7)	23 (79.3)	22 (73.3)
Not evaluable	18 (20.5)	NR	3 (21.4)	0	0
ORR, N(%) (95% CI)	29 (33.0) (23.3, 43.8)	29 (33.0) (23.3, 43.8)	(28.6) (8.4, 58.1)	(10.3) (2.2, 27.4)	7 (23.3) (9.9, 42.3)
Median DOR Median (months) (95% CI)	NE (18.0,NE) [N=29 responders]	NE (18.0,NE) [N=29 responders]	1.7 (0.5, 3.0)	1.9 (1.3, 2.1)	3.3
DRR - 6 mths, % (95% CI)	30.6 (21.0, 40.3)	NR	0 (0.0, 23.2)	0 (0.0, 11.9)	6.7 (0.8, 22.1)

BOR: best overall response; RECIST: response evaluation criteria in solid tumours; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ITT: intent to treat; US: United States; EU: Europe; ORR: objective response rate; DOR: duration of response; DRR: durable response rate; NE: not evaluable; NR: not reported

Source: Table 2.6.1, p103 of the submission

Table 5: Progression Free Survival across the studies

PFS	Avelumab		CTX			
	JAVELIN Merkel 200 Part A 24 month follow-up ITT N=88	Study Obs001 All Qualified		Study Obs001 Immunocompetent		Iyer 2016 N=30 ^b
		Part A (US) N=20	Part B (EU) N=30	Part A (US) N=14	Part B (EU) N=29	
Median PFS Months (95% CI) Min, max	2.7 (1.4, 6.9) 0.03, 35.9+	2.1 (1.0, 3.2)	3.0 (2.6, 3.1)	2.2 (1.2, 3.5)	3.0 (2.5, 3.2)	2.0 (1.3, 2.7) (61 days)
6-mth PFS rate by KM, % (95% CI)	40 (29, 50)	0	2.9 (0.2,13.0)	0	3.4 (0.3, 14.9)	13 (4, 28)
12-mth PFS rate by KM, % (95% CI)	29 (19, 39)	0	0	0	0	0
15-mth PFS rate by KM, % (95% CI)	29 (19, 39)	-	-	-	-	0
24-month PFS rate by KM, % (95% CI)	26 (16, 36)	-	-	-	-	-

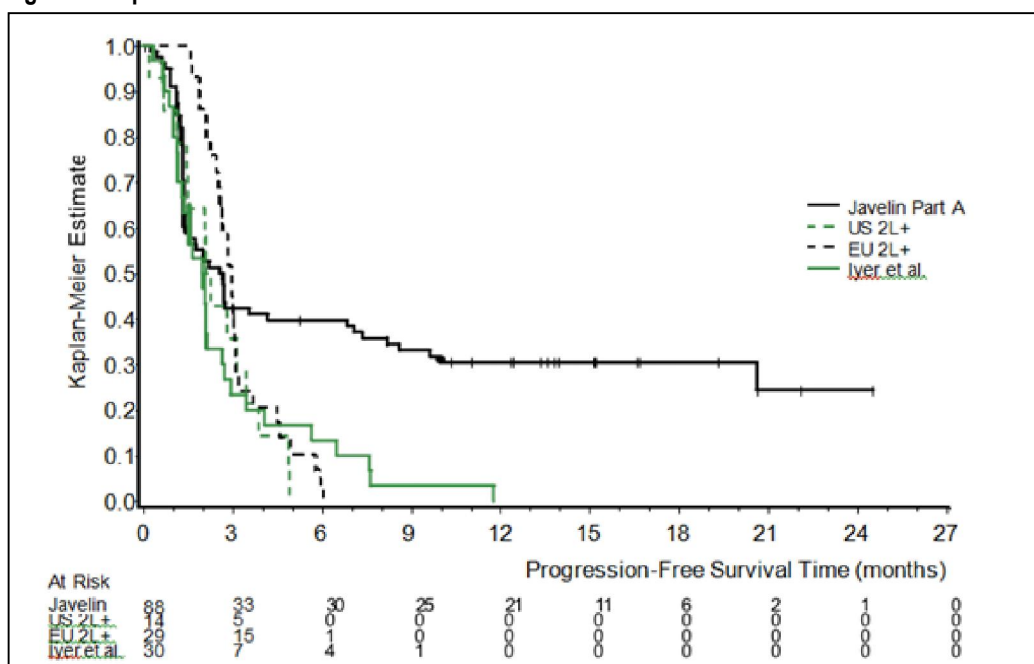
PFS: progression free survival; ITT: intent to treat; US: United States; EU: Europe; KM: Kaplan-Meier estimate; CI: confidence interval.
Source: Table 2.6.3, p108 of the submission.

Table 6: Overall Survival results across the studies

OS	Avelumab		CTX				
	JAVELIN Merkel 200 Part A 18-month follow-up N=88	JAVELIN Merkel 200 Part A 24-month follow-up N=88	Study Obs001 All Qualified		Study Obs001 Immunocompetent ^d		Iyer 2016 (2L) All patients N=30 ^a
			Part A (US) N=20	Part B (EU) N=30	Part A (US) N=14	Part B (EU) N=29	
Median OS Months (95% CI) Min, max	12.6 (7.5, 19.0) 0.4, 30.1	12.6 (7.5, 17.1) 0.4, 35.9+	4.4 (2.2, 6.2)	5.3 (4.3, 5.8)	4.3 (2.1, 6.2)	5.3 (4.3, 6.0)	5.7 35 days – 2.4 years
6-month OS rate by KM, % (95% CI)	70 (59, 78)	70 (59, 78)	30.2 (11.6, 51.4)	26.4 (13.1, 41.8)	26.8 (7.3, 51.5)	27.5 (13.0, 44.2)	NR
12-month OS rate by KM, % (95% CI)	51 (40, 61)	50 (39, 60)	0	0	0	0	NR
15-month OS rate by KM, % (95% CI)	44 (33-54)	43 (32, 53)	NR	NR	NR	NR	NR
18-month OS rate by KM, % (95% CI)	40 (29-50)	39 (29-49)	NR	NR	NR	NR	NR
24-month OS rate by KM, % (95% CI)	-	36 (26-46)	NR	NR	NR	NR	NR

OS: overall survival; US: United States; EU: Europe; KM: Kaplan-Meier estimate; CI: confidence interval; NR: not reported
Source: Table 2.6.5, p112 of the submission

Figure 1: Kaplan Meier PFS estimates across the studies



Source: Figure 2.6.1, p107 of the submission.

- 6.16 The ESC noted that the Kaplan-Meier curves suggest there were different cohorts of patients within the trial (responders/non-responders) and that it appeared there was a prolonged benefit in patients who responded to avelumab.
- 6.17 The submission presented quality of life data using a Visual Analogue Scale (VAS), the EQ-5D Five Level (EQ-5D-5L) and the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) questionnaires. The questionnaires had an approximate response rate of 80% at baseline, which decreased to 60% throughout the treatment period and 34% at the End of Treatment period (p87 of the submission). The submission reported no major change of subject health status over the study period using the VAS and EQ-5D-5L, and small positive score changes in the FACT-M Trial Outcome Index, FACT G Total, and FACT-M Total scores.
- 6.18 There appeared to be an increase in VAS scores along with the FACT-M Trial Outcome Index, FACT-G Total, and FACT-M Total scores over the course of the treatment period. This is likely a reflection of a higher proportion of patients who respond to avelumab remaining on treatment.

Comparative harms

- 6.19 Only safety information for avelumab was reported in the submission. The submission did not make an indirect comparison of harms between avelumab and chemotherapy. An indirect comparison to chemotherapy could not be made based

on the retrospective descriptive study designs of Study Obs001 and Iyer (2016), which did not collect safety information.

6.20 An overview of the safety information from the JAVELIN Merkel 200 study is presented in Table 7.

Table 7: Overview of adverse events in JAVELIN Merkel 200 study (24 month follow-up)

Number of Subjects with any:	Second-line MCC (Part A) 24-month follow-up N=88	First-line MCC (Part B) 3-month follow-up N = 74
	n (%)	n (%)
TEAE ^a	86 (97.7)	67 (90.5)
Related TEAE ^b	67 (76.1)	54 (73.0)
Serious TEAE	45 (51.1)	27 (36.5)
Related serious TEAE	7 (8.0)	8 (10.8)
TEAE, Grade ≥3 ^c	63 (71.6)	28 (37.8)
Related TEAE, Grade ≥3	10 (11.4)	10 (13.5)
TEAE leading to death	13 (14.8)	5 (6.8)
Related TEAE leading to death	0 (0.0)	0 (0.0)
TEAE leading to permanent treatment discontinuation	8 (9.1)	14 (18.9)
Related TEAE leading to treatment discontinuation	6 (6.8)	10 (13.5)
Treatment-emergent immune related AE ^d	17 (19.3)	6 (15.4) ^g
Related treatment-emergent immune related AE ^d	15 (17.0)	3 (7.7) ^g
Treatment-emergent IRR ^e	19 (21.6)	10 (25.6) ^g
Related treatment-emergent IRR ^{e,f}	19 (21.6)	9 (23.1) ^g

MCC: Merkel cell carcinoma; TEAE: treatment emergent adverse event; AE: adverse event; IRR: infusion related reaction;

a TEAEs are defined as events that started during the time from the first dose of study drug to the last dose date + 30 days or earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurred first.

b Related TEAEs are defined as events with a relationship of missing, unknown, or yes.

c Compared to previous data with cut-off 30 December 2016, 3 new subjects experienced treatment related Grade ≥ 3 TEAEs with lipase increased blood creatine phosphokinase increased/troponin increased and polyneuropathy in malignant disease/paraneoplastic encephalomyelitis.

d irAEs were identified according to a 2-level approach using predefined MedDRA Preferred Term queries as well as medical review evaluating corticosteroid use and possible alternative etiologies.

e Infusion-related reactions were identified using MedDRA Preferred Terms of infusion-related reaction, drug hypersensitivity, anaphylactic reaction, hypersensitivity, Type 1 hypersensitivity, and additional potential symptoms of infusion reactions (preferred Terms of pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria) occurring on the day of the infusion and resolving within 2 days.

f Only one related treatment-emergent IRR was Grade 3, the event occurred during the second avelumab infusion

g These were not reported in the 24 month preliminary report so taken from JAVELIN Merkel 200 Addendum 4 Supplementary Tables and Figures Table 15.3.1.20 p70.

Source: Table 2.5.8, p93 of the submission

Benefits/harms

6.21 The naïve indirect comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of avelumab and chemotherapy. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.22 The submission described avelumab as superior in terms of effectiveness compared with chemotherapy and non-inferior in terms of safety compared to chemotherapy.

- 6.23 The ESC agreed that the therapeutic conclusion regarding efficacy presented in the submission is adequately supported by the evidence; however, ESC also considered that the magnitude of the efficacy gain is uncertain. This is due to:
- No head-to-head RCT was available.
 - There was no patient matching between these studies and the results may be biased due to observed and unobserved confounders. Consequently, the risk of bias across the studies was considered to be high.
 - The sample sizes in the studies were low.
 - The OS data in the second-line setting were immature. At 18 months 61% of patients had died. The PSCR provided data at 24 months where 63.6% patients had died, with a median OS of 12.6 months (95% CI: 7.5, 17.1). The PSCR noted that only two additional patients had died between the 18 month data cut-off and 24 month data cut-off, and argued that this was evidence that OS in the second-line and later population was stable. The ESC noted that longer follow-up is required for the estimate of OS to be more reliable. The pre-PBAC response argued that a maximum follow-up of more than 36 months in a condition that the TGA noted has no established therapies and a life expectancy of less than 6 months could be considered long-term data.
 - Efficacy data from the JAVELIN Merkel 200 study in the first-line setting were immature. At 3 months 11% of patients had died. In the pre-PBAC response the sponsor agreed that the data in first line is emerging, but reiterated that the data currently available suggest avelumab may provide greater benefit in the first line setting than in the second line setting. The PBAC noted that the sponsor is committed to providing ongoing efficacy and safety data. The PBAC considered that these data should be provided to the PBAC when available.
- 6.24 It is possible that the safety profile of avelumab is superior to that of chemotherapy, however this remains uncertain given a formal comparison was not possible. The PSCR stated that while a formal assessment of the comparative safety was not possible; the TGA Delegate's Overview considered that for most patients (especially the elderly with comorbid conditions), avelumab is probably more tolerable than platinum-based chemotherapy.
- 6.25 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.26 The PBAC considered that the claim of non-inferior comparative safety between avelumab and chemotherapy was likely to be reasonable given the different mechanisms of action and noted this was consistent with the TGA Delegate's view.

Economic analysis

- 6.27 The submission presented a cost-effectiveness and cost-utility analysis to estimate the cost-effectiveness of avelumab, with the incremental cost per quality adjusted life year (QALY) gained as the main outcome of the evaluation.
- 6.28 The submission fitted parametric functions to the observed data from the JAVELIN Merkel (Part A) study and Study Obs001 to model and extrapolate beyond study follow-up. This was used to estimate the costs and benefits of treatment in avelumab and chemotherapy regimens in the model.
- 6.29 A summary of the model, key drivers and results of the stepped evaluation is provided in Table 8 to Table 10.

Table 8: Summary of model structure and rationale

Component	Description	Justification/comments
Type of analysis	Cost-effectiveness analysis Cost-utility analysis	This is appropriate.
Outcomes	Life years gained, quality-adjusted life years	This is reasonable.
Time horizon	7 years in the model base case (vs. minimum 24 months follow-up for subjects in the JAVELIN Merkel 200 study (Part A), 26 September 2017).	A 24-month OS rate of 36% (95% CI: 26-46) was experienced for patients on 2L+ avelumab, with follow-up still ongoing. The 12-month OS rate of 2L+ CTX treatment was 0%. Approximately 14.6% of avelumab patients were projected to be alive at 7 years.
Methods used to generate results	Partitioned survival model	This approach is commonly used in the economic modelling of oncology interventions.
Health states	Three health states: Progression free (PF): - PF on treatment - PF off treatment Progressed disease (PP): - PP on treatment - PP off treatment Death	A 3 health-state economic model is commonly used in oncology. This model structure is reasonable
Cycle length	7 days	The submissions stated that a cycle length of one week was sufficient to capture the speed of progression of mMCC (p136 of the submission). This is appropriate
Proportion of patients in each health state	Avelumab, PFS: a spline 3 knot-odds function fitted to JAVELIN Merkel study (Part A) Kaplan-Meier data (24 March 2017 cut-off).	The submission did not apply the Kaplan-Meier data directly, and provided no justification for using only the fitted extrapolated data. The submission stated that standard parametric models were not considered to be suitable for extrapolation due to the log-cumulative hazard plots of PFS from the JAVELIN Merkel (Part A) study displaying non-monotonic hazard functions (p140-141 of the submission). This appears reasonable, although it would still be preferable to fit the standard parametric functions for comparison purposes. The submission did not explore fitting a gamma and Gompertz function.
	Avelumab, OS: a spline 1 knot-odds function	The submission did not apply the Kaplan-Meier data

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Component	Description	Justification/comments
	<p>fitted to JAVELIN Merkel study (Part A) Kaplan-Meier data (24 March 2017 cut-off).</p> <p>Modelling constraints included capping PFS with the OS curve and adjusting raw extrapolation estimates to account for the hazard of death seen in the Australian general population mortality data.</p> <p>The projections were adjusted within the economic model to avoid over-estimation versus the predicted OS for avelumab patients.</p>	<p>directly, and provided no justification for using only the fitted extrapolated data.</p> <p>The submission stated that standard parametric models were not considered to be suitable for extrapolation due to the log-cumulative hazard plots of PFS from the JAVELIN Merkel (Part A) study displaying non-monotonic hazard functions (p140-141 of the submission). This appears reasonable, although it would still be preferable to fit the standard parametric functions for comparison purposes. The submission did not explore fitting a gamma and Gompertz function.</p>
	<p>Chemotherapy, PFS: a Weibull function fitted to Study Obs001 Part B Kaplan-Meier data.</p>	<p>The submission did not apply the Kaplan-Meier data directly, and provided no justification for using only the fitted extrapolated data.</p> <p>This function appears reasonable.</p>
	<p>Chemotherapy, OS: a Gompertz function fitted to Study Obs001 Part B Kaplan-Meier data</p>	<p>The submission did not apply the Kaplan-Meier data directly, and provided no justification for using only the fitted extrapolated data.</p> <p>This function appears reasonable.</p>
	<p>Avelumab time on treatment: a log-logistic function fitted to JAVELIN Merkel 200 (Part A) Kaplan-Meier data. Assumed 5% of patients remain on treatment beyond 2 years, and capped at 5 years. ToT curve assumed to not exceed that of the PFS curve.</p> <p>Chemotherapy time on treatment: assumed that up to six treatment cycles, 3 weeks in length (maximum of 18 weeks) for chemotherapy regimens.</p>	<p>The submission did not apply the Kaplan-Meier data directly, and provided no justification for using only the fitted extrapolated data.</p> <p>The requested PBS restriction states that “patient must have stable or responding disease”. It is likely that patients who respond to therapy will have an extended treatment duration, given the long tail observed in the PFS Kaplan-Meier curves of the JAVELIN Merkel 200 study. Consequently, treatment costs were likely underestimated in the model.</p> <p>The submission did not justify the time on treatment of six cycles chosen for the model and whether this reflects clinical practice in Australia. The submission did not explain why they did not use Study Obs001 data for time on treatment.</p> <p>The PSCR stated the assumption of 6 months on treatment with chemotherapy was based on clinical opinion obtained for the UK for the avelumab NICE submission. The 10 Australian clinicians surveyed as part of the PSCR noted that cycles typically ranged between 4 and 6 cycles, depending on what patients were able to tolerate. The PSCR presented results from a sensitivity analysis of 6 cycles, totalling 12 weeks of treatment; the ICER increases marginally from \$45,000/QALY - \$75,000/QALY to \$45,000/QALY - \$75,000/QALY.</p>
<p>Incidence of adverse events</p>	<p>Avelumab: JAVELIN Merkel 200 study: 3 March 2016 data cut-off.</p>	<p>The incidence of AEs is uncertain as there was a lack of comparative safety data between avelumab and chemotherapy.</p>

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Component	Description	Justification/comments
	<p>Chemotherapy: data were extracted from studies identified in the systematic literature review conducted for the NICE UK submission for each treatment, matching patient characteristics as closely as possible with patients from the JAVELIN Merkel 200 study. The submission estimated the incidence of adverse events with chemotherapy based on the treatment of small-cell lung cancer (SCLC) and melanoma.</p> <p>Submission assumed that AEs not reported during JAVELIN Merkel 200 and Study Obs001 had 0% prevalence.</p>	<p>The submission did not justify why data from different cut-off points from the JAVELIN Merkel 200 study for efficacy and adverse events with avelumab were applied. This favours avelumab as no grade ≥ 3 treatments related adverse events (TRAEs) were reported in $\geq 5\%$ of the patients in the 3 March 2016 data cut-off. However, grade ≥ 3 anaemia was reported in 10.2% of patients, grade ≥ 3 lymphopenia in 6.8% of patients and grade ≥ 3 hypertension in 6.8% of patients in the 24 March 2017. This underestimates disutilities and the costs of adverse events for avelumab. (Refer to paragraph 6.32 below).</p> <p>The incidence of adverse events with chemotherapy is uncertain.</p>
Utilities	<p>Progression free and progressed disease utilities for both avelumab and CTX: Patient-level EQ-5D-5L responses (N=72) from JAVELIN Merkel 200 trial converted using a UK specific scoring algorithm, adjusted using a linear mixed regression model.</p> <p>Disutilities associated with adverse events for both avelumab and CTX were sourced from the literature.</p> <p>The estimated duration for each adverse event was sourced from NICE UK manufacturer submissions for immunotherapy and chemotherapy treatments for metastatic non-small cell lung cancer, melanoma, and other cancers.</p> <p>Disutilities were applied only to patients on treatment, determined by the time on treatment curve for avelumab and the time on treatment from the studies for CTX regimens. The overall disutilities applied at each model cycle (i.e. per week while on treatment) were weighted by the mean duration (in days) of adverse events and weighted according to proportions of chemotherapy regimens used.</p>	<p>The submission did not provide any patient level data or STATA code/output to verify the utility values.</p> <p>The submission did not report how the results were adjusted for differences in utility values based on questionnaires that had missing domain scores or were missing in their entirety.</p> <p>The results may also be subject to bias as the JAVELIN Merkel 200 study was open-label.</p> <p>The utilities estimated using the JAVELIN Merkel 200 study would include the impact of AEs for avelumab. The submission argued that the linear mixed regression model was used to avoid double-counting, however the confounders in the model were not described.</p> <p>The submission did not test the use of the Australian scoring algorithm, which is also available for this instrument.</p> <p>The utilities in the progressed disease health state were based on a single 'end of treatment' observation for a small number of patients (N=20 patients). It is likely that the utility value for the 'post progression' health state maybe over-estimated.</p> <p>The estimated disutilities are uncertain. Due to the lack of literature, the submission assumed some values for adverse events disutilities as well as the duration of adverse events. The duration of the adverse events was based on studies in NICE UK manufacturer submissions and may not reflect the Australian clinical setting.</p>

CTX: chemotherapy; 2L+: second-line therapy; mMCC: metastatic Merkel Cell Carcinoma; LYG: life-year gained; OS: overall survival; PFS: progression-free survival; QALYs: quality-adjusted life-years; QOL: quality of life
Source: Table 2.8.2, p128 of submission.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Time on treatment (ToT)	Treatment beyond confirmed diseases progression was permitted in the JAVELIN Merkel 200 study. Patients were still receiving treatment with avelumab at the 18 month data cut-off used to inform the submission, and a long tail is seen in the PFS Kaplan-Meier curves. It is likely that patients who respond to therapy will have an extended treatment duration. The submission assumed 5% of patients remain on treatment beyond 2 years, with maximum expected treatment of 5 years.	High. Favours avelumab.
Time horizon	A time horizon of 7 years was applied.	High. Favours avelumab.
Costs for subsequent therapies	Costs associated with BSC and subsequent therapies were not included in the economic model. Patients are expected to be on avelumab for a longer period than chemotherapy due to improved survival.	Likely to favour avelumab.

AEs: adverse events; PFS: progression free survival; ToT: time on treatment.

Source: compiled during the evaluation using Section 3.4, pp 139-170 of the submission.

Table 10: Results of the stepped economic evaluation

Steps	Costs			QALYs			ICER
	Avelumab	Chemotherapy	Incremental	Avelumab	Chemotherapy	Incremental	
Step 1: Minimum study follow-up time horizon: 18 months, drug costs only	\$████	\$████	\$████	0.90	0.30	0.59	\$████
Step 2: Minimum study follow-up time horizon: 18 months, all costs	\$████	\$████	\$████	0.90	0.30	0.59	\$████
Step 3: Study data extrapolated to 7-year time horizon, all costs	\$████	\$████	\$████	1.64	0.30	1.33	\$████

ICER: Incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life year.

Source: Table 3.7.2, p190 of the submission.

The redacted table shows ICERs in the range of \$45,000/QALY - \$200,000/QALY.

6.30 The univariate sensitivity analyses conducted by the submission showed that the ICER was most sensitive to the treatment duration and time horizon (see Table 11 for key changes and their impact and Figure 2 for the impact of the model time horizon on the ICER).

Table 11: Results of key sensitivity analyses

Variable or assumption	Base case	Alternative(s)	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Base case	-	-	\$ [REDACTED]	1.33	\$ [REDACTED]
Time horizon	7 years	5 years	\$ [REDACTED]	1.12	\$ [REDACTED]
		10 years	\$ [REDACTED]	1.55	\$ [REDACTED]
		15 years*	\$ [REDACTED]	1.76	\$ [REDACTED]
		20 years*	\$ [REDACTED]	1.88	\$ [REDACTED]
Proportion of patients expected to remain on treatment after 2 years	5%	0%	\$ [REDACTED]	1.33	\$ [REDACTED]
		33%	\$ [REDACTED]	1.33	\$ [REDACTED]
		50%*	\$ [REDACTED]	1.33	\$ [REDACTED]
		100%*	\$ [REDACTED]	1.33	\$ [REDACTED]
Time on Treatment (ToT): Estimated discontinuation time for the majority of patients*	2 years	1	\$ [REDACTED]	1.33	\$ [REDACTED]
		1.5	\$ [REDACTED]	1.33	\$ [REDACTED]
		2.5	\$ [REDACTED]	1.33	\$ [REDACTED]
		3	\$ [REDACTED]	1.33	\$ [REDACTED]
Maximum expected treatment duration*	5 years	3	\$ [REDACTED]	1.33	\$ [REDACTED]
		4	\$ [REDACTED]	1.33	\$ [REDACTED]
		6	\$ [REDACTED]	1.33	\$ [REDACTED]
		7	\$ [REDACTED]	1.33	\$ [REDACTED]

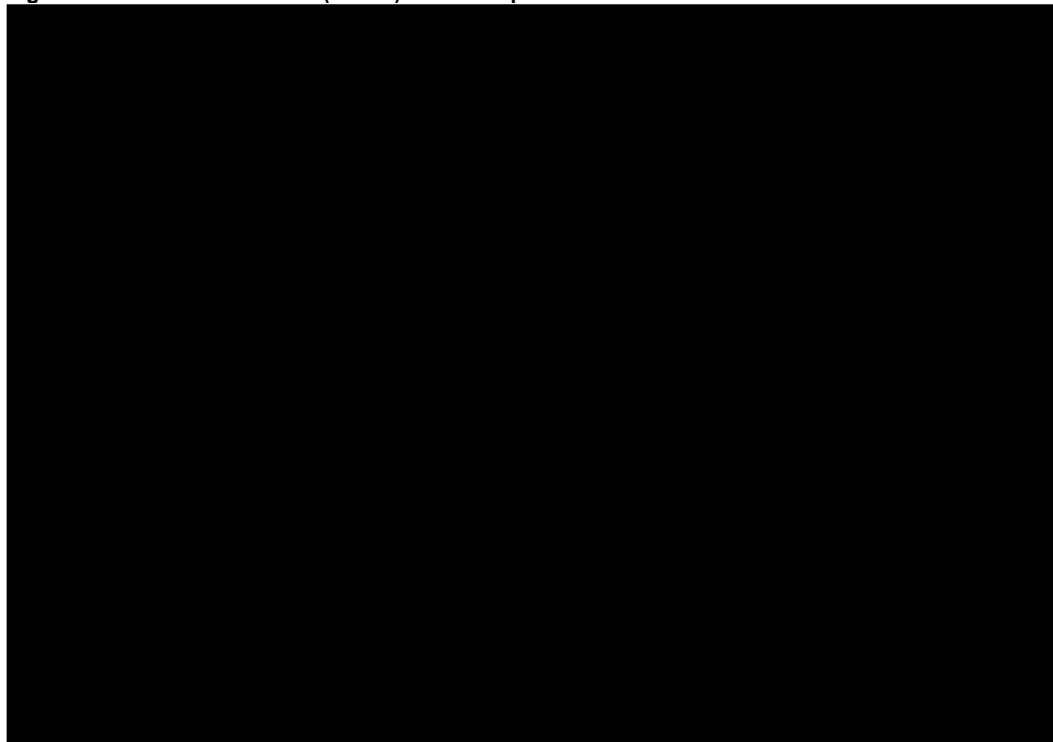
AE: adverse event; ICER: incremental cost-effectiveness ratio PF: progression free survival; PP: Progressed; QALY: quality adjusted life year; OS overall survival.

*Analysis was conducted as part of the evaluation.

Source: Table 3.9.1, p193 of the submission.

The redacted table shows ICERs in the range of \$45,000/QALY - \$105,000/QALY.

Figure 2: JAVELIN Merkel 200 (Part A) data extrapolated to different time horizon VS ICER results



ICER: incremental cost-effectiveness ratio.
Source: conducted during the evaluation.

- 6.31 A time horizon of 7 years was applied in the submission. The ESC noted that having a longer time horizon favours avelumab because more benefits are attributed to avelumab over time. Further, the ESC noted that the time horizon was the main driver of the ICER. The pre-PBAC response argued that a 7 year time horizon was selected to capture the substantially prolonged survival of avelumab compared with chemotherapy (36% of patients alive at 24 months with avelumab compared with 0% alive at 12 months with chemotherapy). The PBAC noted the magnitude of the incremental benefit with avelumab was uncertain given the clinical evidence base, and that extrapolation of the trial results further increased the extent of the uncertainty. The PBAC therefore considered that a 7 year time horizon was not appropriate for the economic model and that a 5 year time horizon should be used for the base case analysis.
- 6.32 The submission only used fitted parametric functions to estimate the proportion of patients in the progression-free and progressed disease health states. The Kaplan-Meier data were not used directly in the economic model. The PSCR claimed that using the Kaplan-Meier data instead of the fitted curves until the median duration of follow-up would have little impact on the ICER. The ESC noted that there was no justification for not using the preferred PBAC approach of applying the Kaplan-Meier data directly in the model followed by extrapolation from median duration of follow up, as the main submission stated that Kaplan-Meier data are available for up to 3 years (September 2017 data cut) (avelumab Commentary, July 2018).
- 6.33 Duration of treatment with avelumab was based on time on treatment in the JAVELIN Merkel 200 trial, extrapolated using a log-logistic function. While the submission assumed the time on treatment did not exceed PFS, the submission also assumed that 5% of patients remain on treatment after two years and continue on treatment until a maximum of five years. However, the requested PBS restriction states that “patient must have stable or responding disease”. It is likely that patients who respond to therapy will have an extended treatment duration, given the long tail observed in the PFS Kaplan-Meier curves of the JAVELIN Merkel 200 study. Consequently, treatment costs were likely underestimated in the model.
- 6.34 In terms of the proportion of patients expected to remain on treatment, the PSCR stated that the base case of the model assumed that 5% of patients on avelumab remain on treatment after two years and continue to a maximum of five years. The PSCR stated when this 5% is increased to 10%, 20%, and 30% the ICER increases from \$45,000/QALY - \$75,000/QALY gained to \$45,000/QALY - \$75,000/QALY. The PSCR acknowledged that although the ICER is sensitive to this model parameter, it was selected to align with the feedback from UK clinicians interviewed that patients are unlikely to want to continue treatment after two years and consistent with the

responses from Australian clinicians. The ESC considered that this claim was uncertain as the results of the Australian clinician survey had a poor response rate. In addition, the ESC noted during the evaluation more extreme sensitivity analyses were conducted on the proportion of patients expected to remain on treatment after 2 years, and when the 5% is increased to 33%, 50% and 100% the ICER increased from \$45,000/QALY - \$75,000/QALY to \$45,000/QALY - \$105,000/QALY.

- 6.35 In terms of time on treatment (ToT), the PSCR stated that the ToT in the model was assumed to not exceed PFS to align with the requested restriction of avelumab, resulting in an ICER of \$45,000/QALY - \$75,000/QALY. The PSCR stated that when ToT is allowed to exceed PFS, the ICER increases marginally to \$45,000/QALY - \$75,000/QALY. The ESC noted the assumptions for this analysis were not provided (including the extent that ToT is assumed to exceed PFS by). The submission proposed a maximum expected treatment duration of 5 years. The ESC considered that this cap on ToT was uncertain and not justified by the submission. Further, ESC noted that the model was sensitive to the time point chosen. Overall, the ESC remained uncertain with regards to the ToT and maximum treatment duration. The PBAC agreed with the ESC that the ToT was uncertain, noting that for those patients with a durable response, treatment may be longer than that used in the model. In particular, the PBAC considered that the average treatment duration would be longer in clinical practice with a listing agnostic to treatment line. The PBAC noted the advice from the clinician at the sponsor hearing that the ideal approach is to treat patients beyond 1 year up to about 2 years, as there is a deepening of response over 1 - 1.5 years. In the pre-PBAC response, the sponsor acknowledged that there is uncertainty around the future treatment duration in the Australian setting, but argued that this uncertainty could be addressed through a RSA.
- 6.36 Costs associated with best supportive care (BSC) and subsequent therapies were not included in the economic model. Patients on avelumab may receive more healthcare (BSC and subsequent therapies) due to improved survival. Consequently, treatment costs are likely to be higher for avelumab. This approach most likely favours avelumab. The PSCR stated that to include costs associated with BSC and subsequent therapies in the economic model for patients on avelumab would possibly double count medical resource use. The PSCR also stated that if a conservative assumption was made that increases the cost of medical resource use for all treatments in the post-progression health states by a factor as large as 10 (\$█ to \$█) the ICER increases marginally from \$45,000/QALY - \$75,000/QALY to \$45,000/QALY - \$75,000/QALY. The ESC noted the assumed medical resource use for the post-progression health state was one GP visit every 2 treatment cycles (2 months) and radiotherapy 1-2 times per year, and that this may not adequately reflect post-progression resource use in Australian clinical practice.
- 6.37 The submission did not justify using data from the JAVELIN Merkel 200 study from different cut-off points for efficacy (24 March 2017) and adverse events (3 March

2016). This favours avelumab as no grade ≥ 3 treatments related adverse events (TRAEs) were reported in $\geq 5\%$ of the patients in the 3 March 2016 data cut-off. Based on the 24th March 2017 data cut-off, grade ≥ 3 anaemia occurred in 10.2% of patients, grade ≥ 3 lymphopenia occurred in 6.8% of patients and grade ≥ 3 hypertension occurred in 6.8% of patients. This underestimates disutilities and the costs of adverse events for avelumab. The PSCR updated the economic model to include the 24 March 2017 data for adverse events. The PSCR stated that the ICER increases marginally from \$45,000/QALY - \$75,000/QALY to \$45,000/QALY - \$75,000/QALY. The ESC noted the revised ICER was not verified.

6.38 The following issues were also identified during the evaluation:

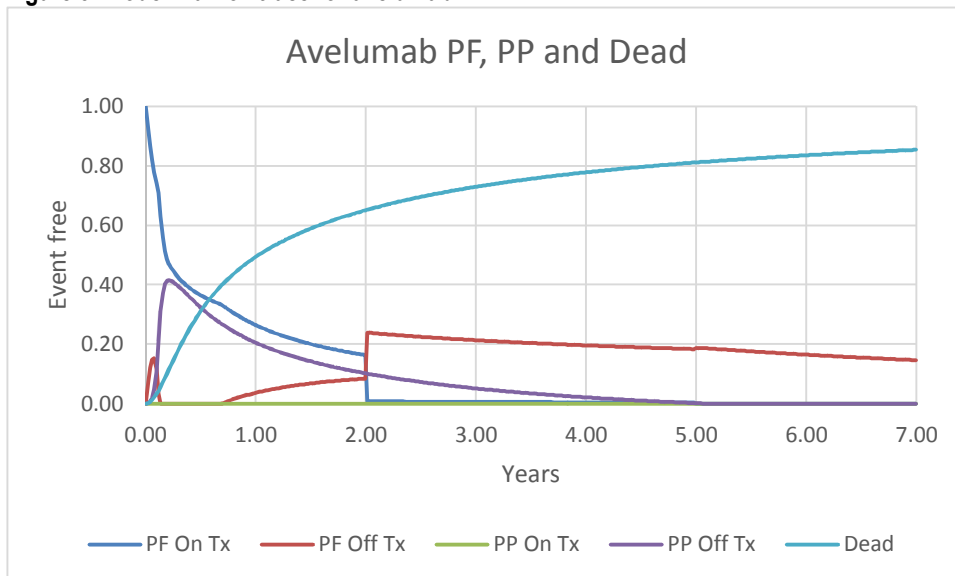
- The clinical data used in the economic model was not based on an RCT, but on non-randomised observational, open-label studies that may be biased due to observed and unobserved confounders.
- The incidence of AEs is uncertain as there was a lack of comparative safety data between avelumab and chemotherapy.
- The submission estimated the incidence of adverse events with chemotherapy based on the treatment of small-cell lung cancer (SCLC) and melanoma.
- The application of disutilities sourced from the literature for SCLC, breast cancer, pancreatic cancer and lymphocytic leukaemia may not be applicable to patients with mMCC in the Australian clinical setting.

6.39 There were several issues with the utility estimates for the pre-progression and progressed disease states:

- The utility estimates from the JAVELIN Merkel 200 study were unable to be verified as patient data or STATA code/output was not provided.
- The submission did not report how the results were adjusted for differences in utility values based on questionnaires that had missing domain scores or were missing in their entirety.
- The results may also be subject to bias as the JAVELIN Merkel 200 study was open-label.
- The utilities estimated using the JAVELIN Merkel 200 study would include the impact of AEs for avelumab. The submission argued that the linear mixed regression model was used to avoid double-counting, however the confounders in the model were not described.
- The submission did not test the use of the Australian scoring algorithm, which is also available for the EQ-5D-5L.
- The utilities in the progressed disease health state were based on a single 'end of treatment' observation for a small number of patients (N=20 patients). It is likely that the utility value for the 'post progression' health state maybe over-estimated.

- The PSCR noted that it was assumed that the UK weights would not be dissimilar in Australia, based on a study by Viney et al and thus for consistency, the utilities were not reanalysed. Varying the utility values of the progression free and post progression health states by +/-10% in sensitivity analysis yields ICERs of \$45,000/QALY - \$75,000/QALY (PSCR). The ESC noted the study by Viney et al includes a graph that depicts the UK algorithm generally results in lower utility values compared to the Australian algorithm.
- 6.40 Markov traces for the avelumab and chemotherapy arms are presented in Figure 3 and Figure 4. The ESC noted PFS and OS for avelumab were extrapolated using spline models. The submission justified spline models on the basis on non-monotonic hazard functions. The ESC considered, based on the available data for the JAVELIN trial, it is difficult to assess if the functions are truly monotonic and a comparison with use of a gamma function for extrapolation would be informative.

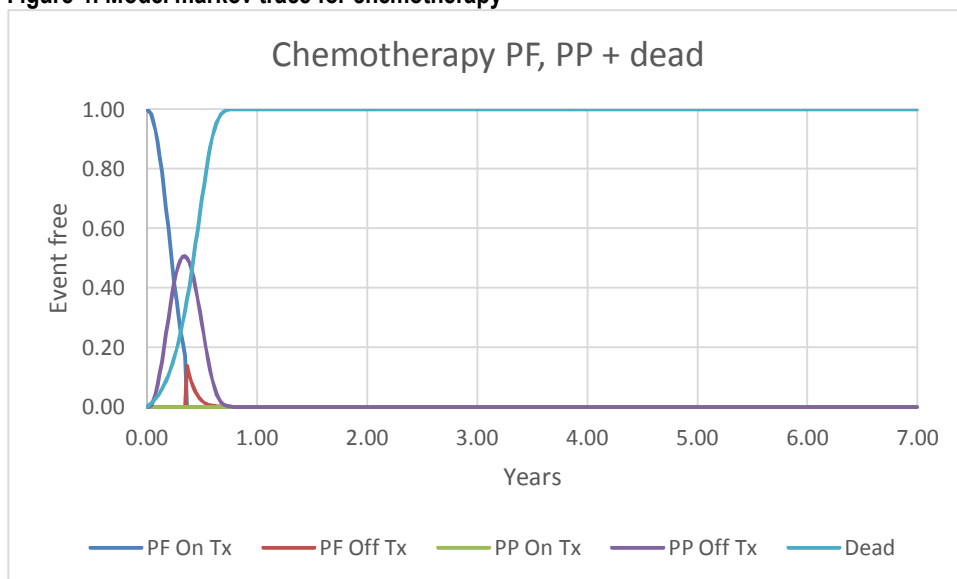
Figure 3: Model markov trace for avelumab



PF on Tx: progression free on treatment; PF off Tx: progression free off treatment; PP on Tx: progressed disease on treatment; PP off Tx: progressed disease off treatment

Source: Sheet 'Section 3 Results Tables' of Attachment 11_CE Model.xlsb of the submission

Figure 4: Model markov trace for chemotherapy



PF on Tx: progression free on treatment; PF off Tx: progression free off treatment; PP on Tx: progressed disease on treatment; PP off Tx: progressed disease off treatment

Source: Sheet 'Section 3 Results Tables' of Attachment 11_CE Model.xlsx of the submission

Drug cost/patient/course: \$ [REDACTED]

6.41 Based on an average dose per treatment of 849.2 mg per person, the dosing frequency being every two weeks, the median duration of treatment of 17 weeks (i.e. 8 treatments) from the JAVELIN Merkel 200 study (Part A), and a cost of \$ [REDACTED] per vial (200 mg vials). However, the PBAC noted that the treatment duration is extrapolated in the model and it is estimated that the mean number of weeks of treatment is 34 weeks, which would approximately double the cost per patient. Noting the uncertainty surrounding treatment duration, the PBAC considered that the average drug cost per patient is likely to be substantially higher than \$ [REDACTED].

Estimated PBS usage & financial implications

6.42 This submission was considered by DUSC. The submission took an epidemiological approach. The DUSC advised that this was reasonable. Key sources for the approach were:

- Incident and prevalent patients: AIHW 2016 Skin Cancer Report
- Treatment utilisation: Nivolumab PSD 2017
- Costs: Proposed cost presented in the submission and PBS listed costs for chemotherapy

6.43 The DUSC noted that the incidence approach used in the submission did not capture patients progressing to metastatic disease who initially presented with earlier stages

of disease. The DUSC considered that the estimate of metastatic MCC patients (52%) was overestimated and noted that the two population based observational studies stated the proportion of patients who died from MCC was 32-33%.

6.44 The estimated use and financial implications for a second-line listing of avelumab are presented in Table 12.

Table 12: Estimated use and financial implications for a second-line listing

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated						
Number of scripts dispensed						
Estimated financial implications of avelumab						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Copayments	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
Estimated financial implications for chemotherapy						
Cost to PBS/RPBS less copayments	-\$	-\$	-\$	-\$	-\$	-\$
Net financial implications						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Net cost to MBS	\$	\$	\$	\$	\$	\$
Other cost to Government (adverse events)	-\$	-\$	-\$	-\$	-\$	-\$
Overall Net cost to Government Health Budget	\$	\$	\$	\$	\$	\$

Source: Table 4.4.1, p207-208 of the submission; Table 4.5.6, p210 of the submission.

6.45 At year 6, the estimated number of patients was less than 10,000 and the total overall net cost to the Government Health Budget was estimated to be \$30 - \$60 million over 6 years for a second-line listing of avelumab. The pre-PBAC response noted that the DUSC considered estimates for the second line setting presented in the submission to be "reasonable or slightly overestimated". The pre-PBAC response also noted that while DUSC had some suggestions on the assumptions underpinning the budget impact model, overall these balanced out such that the estimates are not materially different.

6.46 Due to the promising (yet immature) results of avelumab in the first-line setting, there is potential for leakage of avelumab to treatment naïve patients. This would make the estimates presented in the submission for a second-line only listing an underestimated.

6.47 The DUSC noted that several assumptions in the financial estimates, including the estimate that 60% of incident mMCC patients would fail first line chemotherapy, are uncertain as they were taken from a clinician survey that had a poor response rate, did not indicate which specialties survey responders were from, and did not indicate how participants were recruited. DUSC noted the proportion of patients who failed chemotherapy at 1 year in Study Obs001 was 75%.

6.48 The estimated cost of a line agnostic listing for avelumab is presented in Table 13.

Table 13: Estimated cost of a line agnostic listing for avelumab

	2019	2020	2021	2022	2023	2024
Total patients treated with avelumab (includes patients continuing past first year)	█	█	█	█	█	█
Overall Net Cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Cost to Government for MBS	\$█	\$█	\$█	\$█	\$█	\$█
Other Costs to Government (Adverse Events)	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Overall Net cost to Government Health Budget of listing Drug	\$█	\$█	\$█	\$█	\$█	\$█

Source: Revised during the evaluation.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be \$10 - \$20 million.

6.49 The estimates provided in Tables 12 and 13 used the base case estimates for the proportion of eligible patients that will take up avelumab therapy (█% in Year 1, █% in Year 2 then █% per year thereafter). The DUSC discussed that the uptake of avelumab in eligible patients is likely to be higher than predicted, potentially starting from █% in year 1 and increasing thereafter. The DUSC also advised that given the potential greater efficacy in the first-line setting, patients newly diagnosed with metastatic disease may be more inclined to seek treatment with avelumab than those who would have already failed first-line chemotherapy.

6.50 The budget impact model for a line agnostic listing assumes the same time on treatment as for the proposed second-line listing. The DUSC advised that given the potential greater efficacy in the first-line setting, time on treatment would be greater with a line agnostic listing. DUSC considered the proposed PBS restriction should match the estimated time on treatment in the budget impact model, which is limited to a maximum of 5 years of treatment.

6.51 The DUSC considered that compared to chemotherapy regimens, clinicians may be less likely to cease treatment in patients with a partial response and evidence of disease. In particular, for avelumab as the risk of harms appears to be low, and the time on treatment for PBS listed avelumab is likely to be longer than in the clinical trial.

6.52 At year 6, the estimated number of patients was less than 10,000 and the total overall net cost to the Government Health Budget was estimated to be \$60 - \$100

million over 6 years for a line agnostic listing for avelumab. It is likely that the overall cost to the federal health budget for a line agnostic listing is underestimated.

Quality Use of Medicines

- 6.53 The submission proposed to distribute resources to patients, oncologists, oncology nurses, oncology pharmacists and other healthcare professionals involved in the treatment of patients with MCC.
- 6.54 The quality use of medicines activities are in line with other medications in this class.

Financial Management – Risk Sharing Arrangement

- 6.55 The pre-PBAC response stated a willingness to enter into a risk sharing arrangement (RSA) following a positive recommendation based on patient numbers and cost to mitigate financial risk to the Commonwealth.

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 treatment of Stage IV (metastatic) Merkel cell carcinoma (mMCC). The PBAC were satisfied that for some patients, avelumab treatment improved observed response rates as well as progression free and overall survival rates compared with currently available chemotherapy treatments. The PBAC advised that avelumab should be listed at an incremental cost-effectiveness ratio (ICER) at or below \$45,000 - \$75,000 per quality-adjusted life year gained and that a risk sharing arrangement would need to be entered into to manage uncertainties around the uptake rates and time on treatment.
- 7.2 The PBAC acknowledged that mMCC is an aggressive, rare cancer and there is a high unmet need for new treatments in this condition. Although noting that the data presented, particularly in the first line setting, are limited and immature, the PBAC considered that a listing that enables use in the first line setting would allow equitable access to patients.
- 7.3 The PBAC considered that the sponsor hearing and the consumer comments were informative and provided clinical insight into the current treatment available for this rare condition. The PBAC noted that the comments described avelumab as being more effective and tolerable than chemotherapy and considered that this was particularly important as the average age of patients with MCC is approximately 70 years and these patients are likely to have comorbid diseases that may result in chemotherapy not being well tolerated. There was strong support for a listing of avelumab that includes first line use. The comments also highlighted that PBS listing of avelumab would help with the financial burden of having a rare cancer, and noted

- that there is emerging data for PD-1 inhibitors which demonstrate effectiveness in treating MCC.
- 7.4 The PBAC recommended that avelumab should be available as an Authority Required Streamlined listing under special arrangements under Section 100, Efficient Funding of Chemotherapy program.
 - 7.5 The PBAC considered that a grandfather restriction was not necessary, as patients who are in the early access program for avelumab would meet the criteria in the initial restriction.
 - 7.6 The PBAC considered that the proposed maximum amount (units) of 6 is appropriate in the initial and continuing restrictions. The PBAC considered that a maximum of 8 repeats is appropriate for the initial restriction, and a maximum of 11 repeats is appropriate for the continuing restriction.
 - 7.7 The PBAC recommended that the listing not be restricted based on WHO or ECOG status.
 - 7.8 The PBAC considered that chemotherapy as the main comparator, which is the current Australian standard of care, was appropriate.
 - 7.9 The PBAC noted the phase II JAVELIN Merkel 200 study that was used to support the submission. JAVELIN Merkel 200 is an open label study of patients treated with avelumab in first-line (part B) and second-line (part A) mMCC. A naïve comparison with data from one key retrospective observational cohort study of patients treated with chemotherapy (Obs001, N=121) and one supportive retrospective observational cohort study (Iyer 2016, N=30) was presented in the submission. The PBAC noted that no head-to-head trials were available. The PBAC considered that the evidence presented in the submission was immature, particularly in the first line setting, and the magnitude of benefit was uncertain. However, the Committee also considered that it was unlikely that phase III data would be available in the near future. The PBAC noted that there is emerging phase II data for anti-PD-1 drugs such as nivolumab and pembrolizumab that show this class of drugs are effective in the treatment of MCC.
 - 7.10 The PBAC considered that the claim of superior effectiveness compared with chemotherapy was reasonable. In the second line setting, the PBAC noted PFS at 1 year with avelumab was 30% compared with 0% for standard of care, and OS at 6 months was 70% compared with approximately 30%, and at 12 months was 50% compared with 0%. The PBAC also noted for responders, an extended duration of benefit with the median duration of response not reached in the analysis based on a ≥ 24 months of follow-up. In the first line setting, the PBAC noted that JAVELIN Merkel 200 study part B only had 30 patients and the data was less mature. However, the results were favourable towards avelumab relative to standard of care (Study Obs001 and Iyer 2016) demonstrating improved ORR (50%-51% vs. 29%-55%), a higher CR rate (16%-18% vs. 13%-14%), improved duration of response (11.3

months vs 2.8-6.7 months), and improved 6-month OS (83% vs. 67%). Additionally, the PBAC noted that the durable response rate (DRR) was higher in the first-line cohort (37.4%) than in the second-line and later cohort (29.1%) of the JAVELIN Merkel 200 study, and this is consistent with the claim that avelumab may provide greater benefit in the first-line compared with second-line and later setting. The PBAC noted that this was consistent with the advice from the sponsor hearing.

- 7.11 The PBAC considered that the claim of non-inferior safety compared with chemotherapy was reasonable. Although a formal comparison was not possible given the limited data available, the PBAC noted the different mechanism of action of avelumab versus chemotherapy, and the TGA Delegate's view that for most patients (especially the elderly with comorbid conditions), avelumab is probably more tolerable than platinum-based chemotherapy.
- 7.12 The PBAC noted that the economic model comparing avelumab and chemotherapy was based on non-randomised, observational, open-label studies that may be biased due to observed and unobserved confounders. The PBAC noted that the model was particularly sensitive to the time horizon and the duration of avelumab treatment.
- 7.13 The PBAC noted the magnitude of the incremental benefit with avelumab was uncertain given the clinical evidence base and that extrapolation of the trial results further increased the extent of the uncertainty. The PBAC therefore considered that a 7 year time horizon was not appropriate for the base case analysis and that a 5 year time horizon should be used.
- 7.14 The PBAC considered there was significant uncertainty surrounding the duration of treatment assumed in the model. The PBAC noted the duration of treatment with avelumab was based on time on treatment in the JAVELIN study and extrapolated using a log-logistic function. The submission assumed the time on treatment did not exceed PFS, and that 5% of patients remain on treatment after two years and continue on treatment until a maximum of five years. The PBAC noted ESC's advice that it is likely that patients who respond to therapy will have an extended treatment duration, given the long tail observed in the Kaplan-Meier PFS curves of the JAVELIN study. The PBAC considered that the average treatment duration would be longer in clinical practice with a listing agnostic to treatment line. The PBAC noted the sponsor proposed that the uncertainty associated with the treatment duration be addressed through a risk sharing arrangement (RSA).
- 7.15 The PBAC considered, given the uncertainties associated with the magnitude of the clinical benefit and treatment duration, an ICER at or below \$45,000/QALY - \$75,000/QALY would be required with a model time horizon of 5 years for avelumab to be considered cost-effective.
- 7.16 The PBAC noted estimates of the financial impact were presented in the submission for a second line listing as well as for a line agnostic listing, and that the treatment duration was assumed to be the same for both scenarios. The PBAC also noted DUSC

advised that given the potential greater efficacy in the first-line setting, the average time on treatment may be greater with a line agnostic listing.

- 7.17 The PBAC considered that a RSA would need to be entered into to manage uncertainties around the uptake rates and time on treatment. The PBAC considered the financial caps should be based on the patient numbers estimated in the submission for a line agnostic listing (less than 10,000 patients in year 1 increasing to less than 10,000 patients in year 6) and that the rebate level should be ■■■% for use beyond the caps.
- 7.18 Under section 101(3BA) of the *National Health Act 1953*, the PBAC recommended that avelumab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.19 The PBAC advised that avelumab is not suitable for prescribing by nurse practitioners as antineoplastic agents are currently considered to be out of scope for prescribing by nurse practitioners. Medical practitioners have been included as the appropriate prescriber type in the restriction.
- 7.20 The PBAC recommended that the Early Supply Rule should not apply as it currently does not apply to Section 100 Efficient Funding of Chemotherapy listings.
- 7.21 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Amount (units)	№.of Rpts	Proprietary name	Manufacturer
avelumab 200 mg/10 mL injection, 10 mL vial	6	8	Bavencio®	Merck Serono Australia Pty Ltd
Category / Program:	Section 100 – Efficient funding of chemotherapy			
Prescriber type:	Medical Practitioners			
Episodicity:	-			
Severity:	Stage IV (metastatic)			
Condition:	Merkel Cell Carcinoma			
PBS Indication:	Stage IV (metastatic) Merkel Cell Carcinoma			
Treatment phase:	Initial treatment			
Restriction:	<input checked="" type="checkbox"/> Streamlined			

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Treatment criteria:	-
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition; AND The treatment must not exceed a total of 9 doses at a maximum dose of 10 mg per kg every 2 weeks under this restriction
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Amount (units)	No. of Rpts	Proprietary name	Manufacturer
avelumab 200 mg/10 mL injection, 10 mL vial	6	11	Bavencio®	Merck Serono Australia Pty Ltd
Category / Program:	Section 100 – Efficient funding of chemotherapy			
Prescriber type:	Medical Practitioners			
Episodicity:	-			
Severity:	Stage IV (metastatic)			
Condition:	Merkel Cell Carcinoma			
PBS Indication:	Stage IV (metastatic) Merkel Cell Carcinoma			
Treatment phase:	Continuing treatment			
Restriction:	<input checked="" type="checkbox"/> Streamlined			
Treatment criteria:	-			
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition; AND Patient must have previously received PBS-subsidised treatment with this drug for this condition; AND Patient must have stable or responding disease AND The treatment must not exceed a total of 12 doses at a maximum dose of 10 mg per kg every 2 weeks under this restriction			
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.			

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The Sponsor welcomes the PBAC's decision to recommend avelumab for patients with metastatic MCC, a rare and aggressive skin cancer with high unmet clinical need and will work with the Department of Health towards a PBS listing at the earliest opportunity. The Sponsor would also like to thank the support of the MCC community, especially those who have participated in our clinical trials, including the now fully recruited first-line metastatic MCC trial.