5.10 RETIFANLIMAB, Solution concentrate for I.V. infusion, 500 mg in 20 mL, Zynyz®, SPECIALISED THERAPEUTICS ALIM PTY LTD.

1 Purpose of submission

1.1 The Category 1 submission requested a Section 100 (Efficient Funding of Chemotherapy Program), Authority Required (STREAMLINED) listing for retifanlimab for the treatment of metastatic or recurrent, locally advanced Merkel cell carcinoma (MCC) not amenable to curative surgery or radiation.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus avelumab.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Metastatic (Stage IV) Merkel Cell Carcinoma (MCC) or recurrent locally advanced MCC not amenable to curative surgery or radiation therapy.
Intervention	Retifanlimab 500 mg intravenously once every 4 weeks until disease progression, unacceptable toxicity, or up to 24 months.
Comparator	Avelumab 10 mg/kg body weight or 800 mg intravenously every 2 weeks until disease progression or unacceptable toxicity. [a]
Outcomes	Efficacy • Objective response rate • Overall survival • Progression-free survival Safety • Treatment-emergent adverse events (TEAEs) • Treatment-related TEAEs • Serious TEAEs • TEAEs leading to treatment discontinuation • Immune-related adverse events • Infusion-related reactions
Clinical claim	Relative to avelumab, retifanlimab is associated with superior efficacy and superior safety in patients with metastatic MCC.

Source: Table 1, p10 of the submission

[a] In the recurrent locally advanced MCC population (not amenable to curative surgery or radiation therapy), the comparator is standard of care chemotherapy regimens. The submission claimed that due to this being a small population (making up approximately 10% of the proposed population based on the POD1UM-201 study), a formal clinical and cost-effectiveness analysis was not presented.

2 Background

Registration status

2.1 The submission was made under the Therapeutic Goods Administration (TGA) / Pharmaceutical Benefits Advisory Committee (PBAC) Parallel Process. A TGA application was lodged on 30 April 2025 under the Project ORBIS program, and the

delegate's overview was expected in March 2026. Retifanlimab received orphan drug designation for MCC.

2.2 The proposed TGA indication is "for the treatment of adult patients with metastatic or recurrent locally advanced MCC". The TGA Clinical Evaluation Report (CER) – Round 1 was available at the time of PBAC consideration. The Clinical Evaluator had no objection to approval of retifanlimab for this indication.

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

3 Requested listing

3.1 Secretariat suggested additions are in italics and deletions are in strikethrough

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Dispensed price for maximum amount [a]	Proprietary name and manufacturer
Retifanlimab 25 mg/mL 20mL vial	500 mg	5	**Published:** Public: $22,091.23 Private: $22,444.90 **Effective:** Public: $[redacted] Private: $[redacted]	ZYNYZ® Specialised Therapeutics Alim Pty Ltd

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED) NEW
Administrative Advice: *No increase in the maximum amount 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.
Episodicity: BLANK
Severity: *Recurrent locally advanced or Stage IV (metastatic)*
Condition: Merkel Cell Carcinoma
Indication: Recurrent~~,~~ locally advanced ~~disease not amenable to surgery or radiation and~~ *or* Stage IV (metastatic) Merkel Cell Carcinoma
Treatment Phase: ~~All treatment~~
Population criteria:
Patient must have either of the following at treatment initiation: (i) recurrent locally advanced disease not amenable to surgery or radiotherapy, (ii) metastatic disease
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised *systemic anti-cancer* therapy for this condition
AND
Clinical criteria:
The treatment must not exceed a total of *(i) cumulative* 24 months*, (ii) 26 doses* ~~under this restriction~~ *whichever comes first from the first dose of this drug regardless if it was PBS/non-PBS subsidised*
AND
Clinical criteria:
~~Patient who has progressive disease when treated with this drug for this condition is no longer eligible for PBS-subsidised treatment with this drug for this condition.~~ *Patient must not have experienced disease progression while being treated with this drug for this condition*
AND
Clinical criteria: ~~**Notes:** Treatment with a PD-1 and PD-L1 for this condition is limited to once per lifetime of the patient.~~
Patient must be untreated with programmed cell death-1/ligand 1 (PD-1/PD-L1) inhibitor therapy at initiation therapy for this indication;
~~**Notes:** Patients who have developed intolerance to avelumab of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised retifanlimab~~

3.2 A special pricing arrangement (SPA) was requested for retifanlimab with a published approved ex-manufacturer price (AEMP) of $22,000 per 500 mg vial and an effective AEMP of $[redacted] per 500 mg vial.

3.3 As flat based dosing was proposed, the Secretariat suggested including no increases to quantity/amount be added to the restrictions.

3.4 The proposed restriction is broader than the existing avelumab PBS indication, which is limited to patients with metastatic (Stage IV) MCC, whereas the requested listing for retifanlimab also includes recurrent locally advanced disease not amenable to surgery or radiation. No comparative clinical evidence or economic evaluation was presented for this population, as the submission claimed it is expected to be small (approximately 10%) based on the POD1UM-201 study (10 of 101 chemotherapy naïve patients). The submission requested that the PBAC consider a broader listing extended to these patients given the high clinical need in recurrent locally advanced MCC not amenable to surgery or radiation. The ESC considered it likely that avelumab is already being used in a significant proportion of the unresectable locally advanced population, as these patients (with unresectable disease) are essentially managed the same as for patients with metastatic patients in clinical practice.

3.5 The proposed indication was broader than the POD1UM-201 study, which enrolled only patients with Eastern Cooperative Oncology Group (ECOG) performance status 0-1, excluded immunosuppressed patients and patients with prior systemic therapy, including chemotherapy and prior Programmed Death 1 (PD-1) and Programmed Death Ligand (PD-L1) inhibitor therapy. The omission of ECOG performance status in the restriction was consistent with the current restriction of avelumab, which the DUSC and ESC considered reasonable.

3.6 The submission proposed a restriction requirement that patients to be untreated with PD-1 and PD-L1 inhibitors at initiation for this indication, stating that "no trial evidence exist to date describing the efficacy and safety of subsequent use of a PD-1 and PD-L1 in the proposed patient population". However, the proposed restriction included a clause for patients who have developed intolerance to avelumab to receive PBS subsidised retifanlimab. The submission proposed that the same criteria (vice versa) be included in an amended avelumab restriction. However, the ESC and DUSC considered that treatment switching may not be reasonable, as there was no clinical evidence provided for the sequential usage of retifanlimab and avelumab (patients enrolled in POD1UM-1 were required to be naïve to PD-(L)1 inhibitor treatment), and no current restriction allows switching between PD-(L)1 therapies for reasons of intolerance or convenience. Further, the ESC noted switching due to immune adverse events (AEs) was not reasonable as they are likely to occur with alternative PD-L1s/PD-1s.

3.7 The proposed restriction included a criterion that "The treatment must not exceed a total of 24 months…", however the Secretariat recommended specifying this as a cumulative 24 months (or 26 doses) in order to account for any breaks in treatment.

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

4 Population and disease

4.1 MCC, also known as primary cutaneous neuroendocrine carcinoma, is a rare and aggressive neuroendocrine tumour of the skin. Australia has the highest incidence of MCC in the world, which may be associated with the higher UV index compared with

other countries (Wang 2023)[1]. Studies investigating the incidence of MCC across Queensland, Victoria and Western Australia reported incidence rates of 0.8 – 2.5 per 100,000, compared to a global incidence of 0.6 new cases per 100,000 people (Li 2024)[2].

4.2 Characteristics of Australian patients with MCC (any stage) show a higher proportion of males (59%–69%) than females, a median age of diagnosis between 77–79 years, and the most common site at diagnosis being the face/ears.[3,4,5] Most patients in Australia are diagnosed with stage I/II disease (57% to 85%, Wang 2023 and Girschik 2011, respectively).

4.3 The evaluation noted that Marcos 2022[6] reported a retrospective analysis of patients with MCC (N=2010) from the Surveillance, Epidemiology and End Results (SEER) database between 2000 and 2018. The five-year survival was 17.2% for patients with any type of distant metastases (excluding only bone metastasis). Survival for patients without distant metastases or only regional (lymph node) disease was higher, with a 64.4% and 50.7% five-year survival, respectively. However, the evaluation considered that most survival outcomes described in this study may be underestimated as it preceded the availability of immunotherapy treatment in MCC.

4.4 The proposed clinical management algorithm included the addition of retifanlimab in first-line (1L) as an alternative to chemotherapy for recurrent, locally advanced MCC (not amenable for surgery or radiation) and as an alternative to avelumab for metastatic MCC.

4.5 Retifanlimab is a humanised, hinge-stabilised immunoglobulin (Ig) G4κ, anti-PD-1 antibody. Retifanlimab binds to the PD-1 receptor, blocks interaction with its ligands programmed cell death-ligand 1 (PD-L1) and PD-L2, and potentiates T-cell activity. The nominated comparator, avelumab, is a PD-L1 inhibitor and as such has a similar mechanism of action to retifanlimab in blocking the interaction of PD-L1 with its receptor and potentiating T-cell activity.

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

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[1] Wang AJ, et al. 2023. Merkel cell carcinoma: a forty-year experience at the Peter MacCallum Cancer Centre. BMC Cancer 23(1): 30. Available at: 10.1186/s12885-022-10349-1.

[2] Li Z, et al. 2024. Current status of Merkel cell carcinoma: Epidemiology, pathogenesis and prognostic factors. Virology 599: 110186. Available at: https://doi.org/10.1016/j.virol.2024.110186.

[3] Garbutcheon-Singh KB, et al. 2020. Trends in the incidence of Merkel cell carcinoma in Victoria, Australia, between 1986 and 2016. Australas J Dermatol 61(1): e34-e38. Available at: 10.1111/ajd.13131.

[4] Xu W, et al. 2025. e21593 Outcomes of Merkel cell carcinoma: A 10-year population-based study in Queensland, Australia. American Society of Clinical Oncology (ASCO).

[5] Girschik J, et al. 2011. Merkel cell carcinoma in Western Australia: a population-based study of incidence and survival. British Journal of Dermatology 165(5): 1051-1057. Available at: 10.1111/j.1365-2133.2011.10493.x (accessed 4/15/2025).

[6] Marcos R. Gonzalez, et al. 2022. Treatment and survival outcomes in metastatic Merkel cell carcinoma: Analysis of 2010 patients from the SEER database. Available at: https://doi.org/10.1016/j.ctarc.2022.100665

5 Comparator

5.1 The submission nominated avelumab as the main comparator in metastatic MCC.

5.2 In Australia, current first-line treatment of patients with metastatic MCC consists of avelumab, which is listed on the PBS specifically for these patients. Avelumab has a line agnostic listing and therefore may be used in 1L or later lines of therapy, however, the submission assumed that the majority of patients would use avelumab in 1L. The evaluation considered that this was reasonable, as the PBAC previously considered that clinicians would likely preference use in the 1L setting, given the low efficacy and high toxicity in using chemotherapy to treat metastatic MCC (paragraph 2.2, avelumab Public Summary Document [PSD], July 2018 PBAC Meeting). The ESC considered that the nominated comparator of avelumab was reasonable for the metastatic MCC population.

5.3 In patients with recurrent, locally advanced MCC (not amenable to surgery or RT), there are currently no PBS-listed immunotherapies, meaning patients are limited to 1L treatment with standard of care (SoC) chemotherapy. As such, the submission stated that SoC chemotherapy is the comparator for this population, which the evaluation considered reasonable. However, no formal clinical comparison or cost effectiveness analysis of retifanlimab compared with chemotherapy was presented by the submission. Moreover, the ESC considered it very likely that avelumab is currently being used in these patients (see also paragraph 3.4). The submission and the ESC noted the eviQ guidelines (as well as the National Comprehensive Cancer Network [NCCN] and European Society For Medical Oncology [ESMO] guidelines) recommend avelumab for unresectable MCC; however the TGA indication for avelumab is currently limited to metastatic MCC. The submission and the ESC noted other regimens recommended to treat MCC presented in NCCN and ESMO guidelines include nivolumab and pembrolizumab:

- Nivolumab is not TGA-approved for the proposed indication and is not currently undergoing TGA evaluation. The ESC noted that at its September 2025 intracycle meeting, the PBAC considered a proposal for nivolumab + ipilimumab as an 'expanded listing to facilitate broad access for the treatment of unresectable advanced and metastatic cancer'[7]. At that meeting "The PBAC recommended a multi-indication (broad) listing for nivolumab and ipilimumab in advanced or metastatic cancers"[8].

[7] https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/agenda/september-2025-pbac-intracycle-meeting

[8] Recommendations made by the PBAC – September 2025 Intracycle Meeting; https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/recommendations-made-by-the-pbac-september-2025

- Pembrolizumab was approved by the TGA in July 2025 for the treatment (as monotherapy) of recurrent locally advanced or metastatic MCC in patients 12 years and older.

However, these were not considered as near-market comparators by the submission.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (4), health care professionals (7) and organisations (5) via the Consumer Comments facility on the PBS website. The PBAC noted the advice received from Rare Cancers Australia, NeuroEndocrine Cancer Australia, Melanoma & Skin Cancer Advocacy network, Melanoma and Skin Cancer Trials Limited clarifying the likely use of retifanlimab in clinical practice. Input noted limited treatment options for MCC, indicating that there is a clinical need for new therapies. Comments described potential benefits associated with retifanlimab including less frequent dosing (Q4W), and a faster infusion rate (30 minutes), compared to for avelumab (Q2W dosing and 60 minute infusion), as well as a broader restriction (including locally advanced not amenable to surgery or radiotherapy). Comments suggested that retifanlimab is associated with lower toxicity and infusion reactions, and greater efficacy compared with other immune checkpoint inhibitors. Melanoma and Skin Cancer Trials Limited noted that Australia has the highest global incidence of MCC, which is a rare but highly aggressive neuroendocrine skin cancer.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the retifanlimab submission, categorising it as one of the therapies of "high priority for PBS listing" on the basis of an objective response rate (ORR) of 55% in the POD1UM-201 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for retifanlimab, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement) [9], based on the single arm trial.

Clinical studies

6.4 The submission was based on two single arm, Phase 2 studies of retifanlimab (POD1UM-201) and avelumab (JM200 Part B) in adults with MCC. The POD1UM-201

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

study included metastatic and recurrent locally advanced MCC patients (not amenable to curative surgery or radiation) (N=107). Six patients in POD1UM-201 were not chemotherapy naïve, and 10 chemotherapy naïve patients had locally advanced disease. Only the chemotherapy naïve metastatic population of POD1UM-201 (n=91) was used in the indirect comparisons with avelumab. JM200 study enrolled patients with chemotherapy-naïve metastatic MCC (N=116)

6.5 The JM200 Part B study (three months of follow-up only) was previously considered at the July 2018 PBAC Meeting for avelumab for the treatment of metastatic MCC. This submission presented data with longer follow-up from JM200 Part B, including the primary analysis, which assessed all efficacy and safety outcomes at 21.2 month follow-up (data cutoff date of 2 May 2019) (D'Angelo 2021); and the updated analysis of overall survival (OS) at a 54.3-months follow-up (data cutoff date of 21 January 2022) (D'Angelo 2024).

6.6 Details of the studies presented in the submission are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
POD1UM-201 NCT03599713	A Phase 2 Study of INCMGA00012 in Participants With Metastatic Merkel Cell Carcinoma (POD1UM-201). Primary analysis.	Clinical study report 24 June 2022
	A Phase 2 Study of INCMGA00012 in Participants With Metastatic Merkel Cell Carcinoma (POD1UM-201). Final analysis.	Clinical study report 14 February 2025
	Grignani G, et al.(2025) Final Results of POD1UM-201, a Phase 2 Study of Retifanlimab, a Humanized Anti-PD-1 Antibody, in Patients with Advanced or Metastatic Merkel Cell Carcinoma.	Conference abstract ASCO 2025 Annual Meeting; 9536
	AdRes Health Economics & Outcomes Research. Retifanlimab for the treatment of metastatic Merkel Cell Carcinoma: Matching-Adjusted Indirect Comparison. Technical Report Version 2.1.	MAIC report 19 May 2025
	Grignani, G et al. Phase II study of retifanlimab in patients with recurrent locally advanced or metastatic Merkel cell carcinoma (POD1UM-201).[a]	Journal for ImmunoTherapy of Cancer 2025;13:e012478. doi:10.1136/jitc-2025-012478
JM200 Part B NCT02155647	D'Angelo SP, et al. (2018). Efficacy and Safety of First-line Avelumab Treatment in Patients With Stage IV Metastatic Merkel Cell Carcinoma: a Preplanned Interim Analysis of a Clinical Trial.	JAMA oncology 2018; 4(9): e180077.
	D'Angelo SP, et al. (2021) First-line avelumab in a cohort of 116 patients with metastatic Merkel Cell Carcinoma (JAVELIN Merkel 200): Primary and biomarker analyses of a phase II study.	Journal for ImmunoTherapy of Cancer 2021: 9(7).
	D'Angelo SP, et al. (2024) First-line avelumab treatment in patients with metastatic Merkel Cell Carcinoma: 4-year follow-up from part B of the JAVELIN Merkel 200 study.	ESMO Open 2024: 9(5).
	D'Angelo S, et al. (2019) First-line avelumab treatment in patients with metastatic Merkel Cell Carcinoma: Primary analysis after ≥15 months of follow-up from JAVELIN Merkel 200, a registrational phase 2 trial.	Conference abstract Journal for ImmunoTherapy of Cancer 2019: 7
	Bharmal M et al. Health-related quality of life trajectory of treatment-naïve patients with Merkel Cell Carcinoma receiving avelumab.	Future Oncology 2020; 16(27): 2089-2099.

Source: Table 19, pp49-51 of the submission

a. Identified during evaluation

6.7 The key features of the included studies are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Retifanlimab						
POD1UM-201	107	OL, SA, 35.7 months follow-up [a]	High	Treatment naïve advanced (n=10) Treatment naïve metastatic (n=91) Chemotherapy refractory (n=6)	ORR [b], PFS, OS, Safety	MAIC HRs, applied relative to avelumab arm (POD1UM-201 data not directly used)
Avelumab						
JM200 Part B	116	OL, SA, 21.2 months follow-up (ORR and PFS) 54.3 months follow-up (OS)	High	Treatment naïve metastatic	DOR [b] ORR, PFS, OS, Safety	PFS, OS

Source: Compiled during evaluation using information from Tables 21, 24, 31 and 32 of the submission.
DOR = duration of response; HR = hazard ratio; MAIC = matched adjusted indirect comparison; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SA = single arm
[a] The median study follow-up was not reported in either the primary or final CSR for POD1UM-201, therefore the submission assumed the median follow-up for OS to be equivalent to the median follow-up for the study overall.
[b] Primary outcome. All other outcomes are secondary outcomes.

6.8 POD1UM-201 and JM200 Part B formed the basis of an unanchored matched adjusted indirect comparison (MAIC) of retifanlimab versus avelumab in metastatic MCC on the outcomes of overall survival (OS), progression free survival (PFS) and objective response rate (ORR). Given the single-arm open-label design of the two studies, the evaluation considered that these studies were prone to a high risk of bias. Therefore, the evaluation considered that the comparative efficacy of retifanlimab versus avelumab based on an unanchored MAIC and comparative safety based on an unanchored indirect comparison of these two studies is uncertain.

6.9 No clinical comparison of efficacy for retifanlimab versus SoC chemotherapy was presented in the submission for the locally advanced MCC population.

6.10 The evaluation identified a population-adjusted indirect comparison (PAIC) of avelumab and retifanlimab (Kearney 2025[10]), which it considered relevant to the submission, available as conference abstract only.

Comparative effectiveness

6.11 The OS and PFS results from the POD1UM-201 study are summarised in Table 4. The Kaplan-Meier (KM) OS and PFS curves are shown in Figure 1 and Figure 2, respectively.

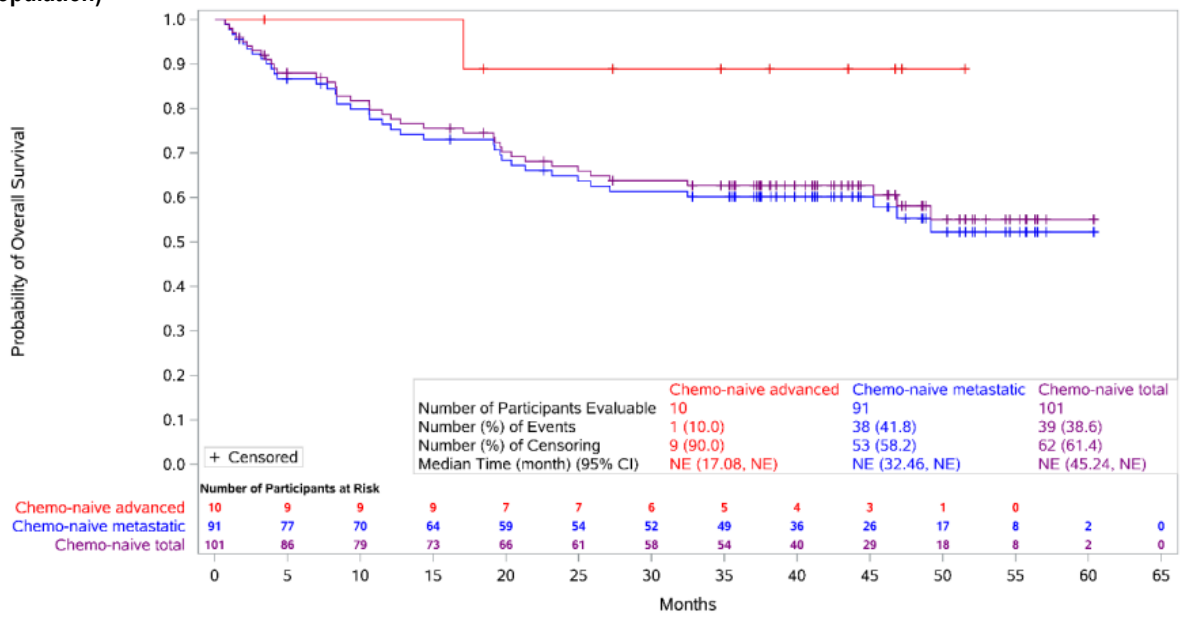
[10] Kearney et al. Population-adjusted indirect comparison (PAIC) of avelumab (AVE) and retifanlimab (RETI) in the first-line (1L) treatment of patients (pts) with metastatic Merkel cell carcinoma (mMCC). Journal of Clinical Oncology June 2025; Volume 43, Number 16_suppl; e21513-e21513

Table 4: Overall survival in the POD1UM-201 study

Treatment arm	Chemo-naïve advanced (N=10)	Chemo-naïve metastatic (N=91)	Chemo-naïve total (N=101)	Chemo-refractory total (N=6)	Total (N=107)
Overall Survival					
Median follow-up (range)	36.4 (3.4, 51.5)	35.7 (0.7, 60.4+)	35.7 (0.7, 60.4+)	25.5 (0.3, 57.5)	35.7 (0.3, 60.4)
Deaths (%)	1 (10.0)	38 (41.8)	39 (38.6)	3 (50.0)	42 (39.3)
Censored (%)	9 (90.0)	53 (58.2)	62 (61.4)	3 (50.0)	65 (60.7)
Median OS (months) (95% CI)	NR (17.08, NE)	NR (32.46, NE)	NR (45.24, NE)	NR (0.26, NE)	NR (45.24, NE)
Progression Free Survival					
Median follow-up (range)	20.8 (1.8, 51.4)	9.0 (0.0, 57.1)	9.3 (0.0, 57.1)	25.5 (0.3, 57.3)	9.3 (0.0, 57.3)
Number (%) of patients with events	3 (30.0)	52 (57.1)	55 (54.5)	3 (50.0)	58 (54.2)
Censored (%)	7 (70.0)	39 (42.9)	46 (45.5)	3 (50.0)	49 (45.8)
Median PFS (months) (95% CI)	NR (1.84, NE)	13.83 (6.74, 27.10)	16.03 (9.03, 32.23)	NE (0.26, NE)	16.03 (9.03, 32.23)

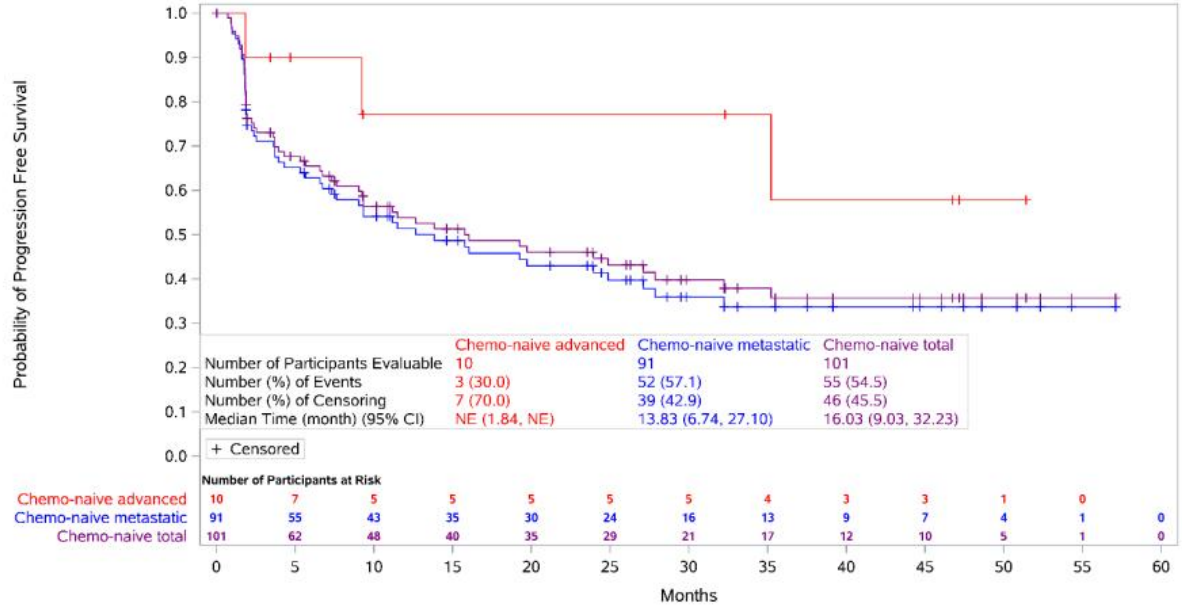
Source: Table 25 and Table 38, p100 and 105 of the submission
CI = confidence interval; NE = not estimable; NR = not reached; OS = overall survival; PFS = progression free survival
Notes: + indicates ongoing response

Figure 1: Kaplan-Meier estimates of overall survival in the POD1UM-201 study (chemotherapy-naïve, safety evaluable population)



Source: Figure 10, p 101 of the submission.
CI = confidence intervals; NE = not estimable

Figure 2: Kaplan-Meier estimates of progression-free survival in POD1UM-201 (chemotherapy-naïve, safety evaluable population)



Source: Figure 12, p106 of the submission
CI = confidence interval; NE = not estimable.

6.12 The KM estimates showed a smaller decline in OS and PFS was observed in the recurrent advanced cohort (n=10) compared with the metastatic cohort (n=91) at all time points. Greater survival benefits in this cohort may be expected given these patients may have less severe disease compared with the metastatic cohort; however, evaluation considered that this comparison should be interpreted with caution given the small sample size of the recurrent locally advanced population.

6.13 The objective response rate (ORR) results from the POD1UM-201 study are summarised in Table 5.

Table 5: Objective response rate and disease control rate based on ICR according to RECIST v1.1 in the POD1UM-201 study (safety evaluable population)

Treatment arm	Chemo-naïve advanced (N=10)	Chemo-naïve metastatic (N=91)	Chemo-naïve total (N=101)	Chemo-refractory total (N=6)	Total (N=107)
Best overall response, n (%)					
CR	3 (30.0)	15 (16.5)	18 (17.8)	1 (16.7)	19 (17.8)
PR	3 (30.0)	34 (37.4)	37 (36.6)	2 (33.3)	39 (36.4)
SD	3 (30.0)	12 (13.2)	15 (14.9)	0 (0.0)	15 (14.0)
PD	1 (10.0)	20 (22.0)	21 (20.8)	0 (0.0)	21 (19.6)
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	2 (1.9)
Missing	0 (0.0)	10 (11.0)	10 (9.9)	1 (16.7)	11 (10.3)
ORR, n (%)	6 (60.0)	49 (53.8)	55 (54.5)	3 (50.0)	58 (54.2)
95% CI for ORR	26.2, 87.8	43.1, 64.4	44.2, 64.4	11.8, 88.2	44.3, 63.9

Source: Table 36, p102 of the submission
CI = confidence interval; CR = complete response; DCR = disease control rate; ICR = Independent Central Review; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

6.14 The submission presented quality of life data using a Visual Analogue Scale (VAS) from the EQ-5D Five Level (EQ-5D-5L) and the Functional Assessment of Cancer Therapy –

Melanoma (FACT-M) questionnaires. Quality of life improved marginally throughout the POD1UM-201 study until end of treatment, where quality of life values fell below baseline levels. The submission claimed this would be expected, given patients are likely to cease treatment once they have experienced progressed disease or intolerable toxicity. The submission did not utilise quality-of-life data from POD1UM-201 in the economic model (see Table 10).

6.15 The unadjusted unanchored indirect comparison for the outcomes of OS, PFS and ORR in POD1UM-201 (metastatic patients, n=91) and JM200 Part B are summarised in Table 6.

Table 6: Unanchored comparison of retifanlimab versus avelumab

Study ID	**POD1UM-201**	**JM200 Part B**	
Treatment arm	**Retifanlimab (N=91)**	**Avelumab (N=116) [primary analysis]**	**Avelumab (N=116) [updated OS]**
Overall Survival			
Median follow-up, months	35.7	21.2	54.3
Median OS (months) (95% CI)	NR (32.46, NE)	20.3 (12.4, NE)	20.3 (12.4, 42.0)
Month 6 OS rate, % (95% CI)	87 (78, 92)	75 (66, 82)	75 (66, 82)
Month 12 OS rate, % (95% CI)	76 (66, 84)	60 (50, 68)	60 (50, 68)
Month 24 OS rate, % (95% CI)	65 (54, 74)	NR	49 (40, 58)
Month 36 OS rate, % (95% CI)	60 (49, 70)	NR	44 (34, 53)
Month 48 OS rate, % (95% CI)	55 (43, 66)	NR	38 (29, 47)
Progression Free Survival			
Median PFS (months) (95% CI)	13.83 (6.74, 27.10)	4.1 (1.4, 6.1)	NR
Median follow-up (range)	9.0 (0.0, 57.1)	NR	NR
Month 6 PFS rate, % (95% CI)	63 (52, 72)	41 (32, 50)	NR
Month 12 PFS rate, % (95% CI)	51 (40, 62)	31 (23, 40)	NR
Best overall response, n (%)			
CR	15 (16.5)	19 (16.4)	NR
PR	34 (37.4)	27 (23.3)	NR
SD	12 (13.2)	12 (10.3)	NR
PD	20 (22.0)	48 (41.4)	NR
Missing	10 (11.0)	9 (7.8)	NR
Objective response, n (%)	49 (53.8)	46 (39.7)	NR
95% CI for ORR	43.1, 64.4	30.7, 49.2	NR
Number (%) of participants who had a response	49 (53.8)	46 (39.7)	NR

Source: Tables 58 – 61, pp141-145 of the submission

CI = confidence intervals; CR = complete response; DCR = disease control rate; NE = not estimable; NR = not reported; ORR = objective response rate; OS = overall survival; PD = progressed disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

6.16 The evaluation and the ESC considered that the following differences in trial and patient characteristics, would have favoured retifanlimab in an indirect comparison:

- More patients treated with retifanlimab had an ECOG PS of 0 than those treated with avelumab (70.3% vs 62.1%, respectively), and therefore may be healthier on average;
- More patients treated with retifanlimab recorded a positive Merkel cell polyomavirus (MCPyV) status than in those treated with avelumab (72.5% vs 60.3%, respectively), and positive MCPyV status may be associated with improved

survival, although studies that have investigated the impact of MCPyV on OS are inconsistent, reporting either a positive correlation or no association[11]; and

- Fewer patients treated with retifanlimab recorded visceral metastases at baseline than those treated with avelumab (31.9% vs 68.1%, respectively), which may suggest less severe disease at baseline.

6.17 Two MAICs were presented in the submission (summarised in Table 7). These were constructed using individual patient data (IPD) from the POD1UM-201 (chemotherapy naïve metastatic cohort n=91), and aggregate data available for the JM200 Part B study, and based on clinical expert opinion of prognostic factors or treatment effect modifiers in MCC.

6.18 Other limitations to both the MAIC1 and MAIC2 analyses included:

- It was not possible to adjust for all known prognostic factors and effect modifiers, as they were not available or there was insufficient overlap between study populations.
- Differences in follow-up time between studies may impact the results, particularly for time-to-event endpoints. Retifanlimab had longer follow-up for PFS, which could lead to more events being captured and potentially underestimate treatment benefit. In contrast, shorter OS follow-up in retifanlimab may result in fewer deaths being observed, possibly overestimating survival.
- The evaluation considered that small values for ESS (after matching) indicated that the weights are highly variable due to a lack of patients available for matching, and so the MAIC estimates may be unstable. The MAIC 1 and MAIC 2 had an informational value of approximately 46% (41/91) and 39.6% (36/91) respectively, which was less than half of the original POD1UM-201 study.

6.19 The submission considered that given the median time since initial diagnosis was different between cohorts at baseline (retifanlimab: 4.2 months; avelumab: 10.6 months), the MAIC 2 analysis was more comprehensive in adjusting for population differences (as it included time since diagnosis as a covariate) and may be considered more informative.

6.20 The results for MAIC2 were more favourable for retifanlimab than MAIC1, and resulted in substantial changes to the OS and PFS, which the evaluation considered may not be appropriate given:

- the difference between MAIC1 and MAIC2 were 'low priority' covariates.
- adjustments made in MAIC1 suggested that the retifanlimab treatment effect was likely overestimated compared to the unadjusted model (i.e. PFS and OS hazard ratios (HRs) in MAIC1 was less favourable). However, MAIC2 adjustments shifted results back into favouring retifanlimab, with a substantial magnitude of change

[11] Schadendorf D, et al. (2017), Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs, *European Journal of Cancer,* https://doi.org/10.1016/j.ejca.2016.10.022

in the point estimate (e.g. OS HR decreased from 0.8 to 0.689 and PFS HR decreased from 0.59 to 0.519 for MAIC1 and MAIC2, respectively, though both MAICs reported an OS HR which included the null in the 95% CI, suggesting there was no difference between retifanlimab and avelumab for OS).

- the point estimate for MAIC2 PFS hazard ratio (HR, 0.519) was more favourable for retifanlimab than the unadjusted model (0.535), which lacked face validity given the number of known differences in baseline characteristic between the two studies which were in favour of retifanlimab (e.g. younger with better average ECOG and less visceral metastasis) as confirmed by MAIC1.

6.21 The evaluation considered that the results of MAIC2 was likely driven by the subgroup results of POD1UM-201 for race. Patients with race classified as 'others' (n=23) had substantially better ORR (69.6%, 95% CI 47.1, 86.8) than Caucasians (n=78) (50%, 95%CI 38.5, 61.5), and MAIC2 reduced the proportion of Caucasians relative to the base case (from 81.3% to 64.7%), which improved the efficacy of retifanlimab. However, there was insufficient evidence to suggest that race was a treatment effect modifier.

6.22 Methodology for the PAIC of avelumab and retifanlimab (Kearney 2025 – see paragraph 6.10) could not be assessed fully due to availability as a conference abstract only. Table 7 summarises the key characteristics and results of the submission's MAIC and Kearney 2025.

Table 7: Key characteristics and results of the submission's MAICs and Kearney 2025

	Current submission		Kearney 2025
	MAIC 1	**MAIC 2**	**PAIC**
Retifanlimab data source	POD1UM-201 individual metastatic patient data (n=91) 35.7 months follow up [a]		POD1UM-201 aggregate data follow up (N=91) 17.6 months follow up
Avelumab data source	JM200 Part B aggregate data (N=116) 21.2 months follow up (ORR and PFS) 54.3 months follow up (OS)		JM200 Part B individual patient data (N=116) 54.3 months follow up
Characteristics adjusted for	• Age (< 65 years vs. ≥65 years) • ECOG PS (0 vs 1) • PD-L1 status (≥1% vs neg.) • MCPyV status • Site of primary tumour (skin vs lymph node) • Visceral metastasis at baseline (present vs absent)	All covariates included in MAIC 1 plus additional 'low priority' covariates: • Race (White, Asian, other) • Gender (male vs female) • Time since initial diagnosis (month)	• Age • ECOG PS • Baseline visceral metastases, PD-L1 status • MCPyV status • Assessment schedule matching (to PFS only)
ESS after matching	41	36	
OS results	HR (95% CI) (HRs<1 favour retifanlimab) [b]		
	Unadjusted Cox model: 0.601 (0.404, 0.894) Weighted Cox model 0.800 (0.492, 1.303)	Unadjusted Cox model: 0.601 (0.404, 0.894) Weighted Cox model 0.689 (0.405, 1.172)	Unadjusted: 0.45 (0.28, 0.71) Adjusted: 1.07 (0.64, 1.79)
PFS results	HR (95% CI) (HRs<1 favour retifanlimab) [b]		
	Unadjusted Cox model: 0.535 (0.375, 0.764) Weighted Cox model 0.590 (0.396, 0.881)	Unadjusted Cox model: 0.535 (0.375, 0.764) Weighted Cox model 0.519 (0.343, 0.786)	Unadjusted 0.60 (0.42, 0.86) Adjusted 1.05 (0.72, 1.51)

Source: constructed during evaluation from Kearney 2025 and pp149-158 of the submission

CI = confidence interval; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; HR = hazard ratio; MAIC = matched adjusted indirect comparison; MCPyV = Merkel cell polyomavirus; NR = not reported; OR = odds ratio; ORR = objective response rate; OS = overall survival; PAIC = population adjusted indirect comparison; PD-L1 = programmed cell death ligand 1; PFS = progression free survival

[a] The median study follow-up was not reported in either the primary or final CSR for POD1UM-201, therefore the submission assumed the median follow-up for OS to be equivalent to the median follow-up for the study overall.

[b] HRs reported in Kearney 2025 were inverted so to align directionally with those reported in the submission.

6.23 The submission's MAICs HRs for OS and PFS differed from those reported in Kearney 2025, with the MAIC's weighted model numerically favouring retifanlimab, and the Kearney 2025 adjusted model numerically favouring avelumab. The ESC noted that the overall conclusions were also contradictory, with the submission's MAICs suggesting that retifanlimab was superior to avelumab in PFS and ORR (all 95% confidence intervals [CIs] excluded the null), but Kearney 2025 suggesting that there was no difference between the two in OS, PFS and duration of response (all 95% CIs contained the null).

6.24 The ESC considered that the respective results of the different adjusted indirect comparisons highlighted the high level of uncertainty associated with indirect comparisons with small sample sizes. As such, the ESC considered that no reliable conclusion on the comparative treatment efficacy of retifanlimab compared with avelumab for patients with chemotherapy-naïve metastatic MCC could be made from the available adjusted indirect comparisons, especially one of a claim of superior

effectiveness. However, the evaluation considered that it was plausible that retifanlimab is at least as effective as avelumab in patients with chemotherapy naïve metastatic MCC given the MAIC in the submission and the PAIC by Kearney 2025 supported this, and avelumab and retifanlimab have similar mechanisms of action as PD-(L)1 inhibitors. The Pre-Sub-Committee Response (PSCR) contended that given the lack of details regarding the PAIC, the MAICs presented in the submission provide a more transparent and robust evidentiary basis to support PBAC's decision-making. However, the ESC considered that the inconsistency in HR values emphasised the uncertainties in the MAIC analyses.

Comparative harms

6.25 The submission presented an unadjusted side by side comparison of safety between retifanlimab and avelumab based on the chemotherapy-naïve metastatic cohort of the POD1UM-201 study and the total safety population of the JM200 Part B study. Results from the total POD1UM-201 cohort were also included in Table 8 for comparison.

Table 8: Overview of safety profile: naïve comparison of retifanlimab and avelumab

Study ID	**POD1UM-201**		**JM200 Part B**
Treatment arm	**Retifanlimab (N=107) Total cohort**	**Retifanlimab (N=91) Chemotherapy-naïve metastatic cohort**	**Avelumab (N=116)**
Follow-up	35.7 months		21.2 months
TEAE, n (%)	97 (90.7)	82 (90.1)	116 (100.0)
Related TEAE, n (%)	72 (67.3)	57 (62.6)	94 (81.0)
Serious TEAE, n (%)	28 (26.2)	24 (26.4)	58 (50.0)
Related serious TEAE, n (%)	13 (12.1)	10 (11.0)	17 (14.7)
TEAE, grade ≥3, n (%)	34 (31.8)	30 (33.0)	70 (60.3)
Related TEAE, grade ≥3, n (%)	18 (16.8)	15 (16.5)	21 (18.1)
TEAE/TEAE leading to death, n (%)	4 (3.7)	4 (4.0)	15 (12.9)
TEAE leading to permanent treatment discontinuation, n (%)	38 (35.5)	19 (20.9)	30 (25.9)
Treatment-emergent irAE (any grade), n (%)	38 (35.5)	32 (35.2)	35 (30.2)
Treatment-emergent irAE, grade ≥3, n (%)	12 (11.2)	10 (11.0)	7 (6.0)
Summary of infusion-related reactions (IRR)			
Treatment-emergent IRR (any grade), n (%)	5 (4.7)	3 (3.3)	34 (29.3)
Treatment-emergent IRR (grade ≥ 3), n (%)	2 (1.9)	1 (1.1)	1 (0.9)
Treatment-related IRR (any grade), n (%)	5 (4.7)	3 (3.3)	13 (11.2) [a]
Treatment-related IRR (grade ≥ 3), n (%)	2 (1.9)	1 (1.1)	1 (0.9) [a]

Source: Table 62, Table 65 p146 of the submission.
irAE = immune-related adverse event; IRR = infusion-related reaction; NR = not reported; TEAE = treatment-emergent adverse event.
[a] Extracted from Supplementary Table 9 of D'Angelo 2021 during evaluation.

6.26 There were four (4.0%) fatal treatment emergent adverse events (TEAEs) in the total population of POD1UM-201 (N=107), due to acute respiratory failure, asthenia, concomitant disease progression, and COVID-19, in one patient each. For the fatal TEAE of concomitant disease progression, the Investigator indicated the possible relationship to retifanlimab could not be excluded.

6.27 In the total POD1UM-201 chemotherapy-naïve cohort, the most frequently reported TEAEs were asthenia (21.8%, 22/101), pruritus (21.8%, 22/101) and diarrhoea (18.8%,

19/101). The most frequent grade ≥3 TEAEs were COVID-19 and lipase increase, which occurred in three participants each (3.0%). The most common treatment-related TEAEs in the total chemotherapy-naïve cohort were pruritus (15.8%, 16/101), asthenia (12.9%, 13/101) and diarrhoea (9.9%, 10/101). The incidence of immune related AEs (irAEs) was generally consistent cross the advanced and metastatic cohorts.

6.28 In regard to the unanchored comparison:

- The submission stated there were fewer TEAEs (90.1% versus 100%), serious TEAEs (26.4% versus 50.0%), TEAEs grade ≥ 3 (33.0% versus 60.3%), and fatal TEAEs (4.0% versus 12.9%) in the retifanlimab cohort compared with the avelumab cohort, but that the type of reported TEAEs experienced across the retifanlimab and avelumab cohorts were generally similar (i.e. <5% differences). However, the ESC considered safety results were confounded due to POD1UM patients being younger, fitter, and with less visceral metastasis.
- The ESC noted that there were more irAEs and grade ≥3 irAEs in POD1UM-201 than JM200 Part B (35.2% versus 30.2%; 11% versus 6%, respectively), and more TEAEs leading to discontinuation.
- The submission noted that fewer patients treated with retifanlimab experienced an infusion-related reaction (IRR) (3.3%) compared with avelumab (29.3%). However, given that Grade ≥ 3 IRRs appeared comparable between studies (1%), the evaluation considered it uncertain whether the differences in treatment-emergent IRRs may be confounded. The PSCR maintained that the lower incidence of IRRs observed with retifanlimab compared with avelumab is a benefit of the less frequent dosing regimen associated with retifanlimab (Q4W for 30 minutes vs Q2W for 60 minutes for avelumab). The PSCR noted that given the low incidence of IRRs in patients treated with retifanlimab, routine premedication is not warranted; however, patients treated with avelumab must be premedicated with an antihistamine and paracetamol prior to the first four infusions per the Australian Product Information.

6.29 Overall, the results of the unanchored comparison of safety were difficult to interpret due to differences in baseline characteristics (see paragraph 6.16) and risk of confounding. Notably, patients enrolled in POD1UM-201 were younger and potentially healthier (regarding ECOG scores and disease severity) on average than those enrolled in JM200 Part B, and therefore the evaluation considered that they may have greater tolerability to treatment. However, the direction of bias (if any) was uncertain. In addition, the included studies were both single arm open-label studies, which limited the assessment of AEs as the incremental safety associated with retifanlimab and avelumab could not be derived. The evaluation considered that no informative conclusion could be made on the comparative safety of retifanlimab and avelumab. Acknowledging the low level of evidence available, given retifanlimab and avelumab are both PD-(L)1 inhibitors, the evaluation considered it was plausible that safety may be similar.

Benefits/harms

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

Clinical claim

6.31 The submission described retifanlimab as superior in terms of effectiveness compared to avelumab.

6.32 The ESC considered the claim of superior efficacy was not adequately supported by the clinical evidence presented in the submission as the results of the MAICs, particularly MAIC2, were highly uncertain and unreliable as differences which may not be treatment effect modifiers such as race were included, and likely biased in favour of retifanlimab.

6.33 However, the ESC considered that, based on the evidence presented in the submission, it was plausible that retifanlimab is at least as effective as avelumab in patients with chemotherapy naïve metastatic MCC, also noting, avelumab and retifanlimab had similar mechanisms of action as PD-(L)1 inhibitors.

6.34 The submission described retifanlimab as superior in terms of safety compared to avelumab.

- The ESC considered that this claim was not adequately supported, as the unanchored indirect comparison of safety was difficult to interpret due to differences in baseline characteristics and at risk of confounding. In addition, the included studies were both single arm open-label studies, which limited the assessment of TEAEs as the incremental safety associated with retifanlimab and avelumab could not be derived. However, acknowledging the low level of evidence available, given retifanlimab and avelumab are both PD-(L)1 inhibitors, the ESC considered that it was plausible that safety may be similar. The Pre-PBAC response contended that retifanlimab's less frequent dosing schedule confers superior safety due to "substantially lower incidence of infusion-related reactions (3.3% vs 29.3%)", and also noted practical benefits noted by consumers associated with shorter infusion time (see paragraph 6.2).

6.35 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data, but that it was reasonable to assume non-inferior effectiveness compared to avelumab.

6.36 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data, but that it was reasonable to assume non-inferior safety.

Economic analysis

6.37 The submission presented a cost-utility analysis based on the results of the MAICs of POD1UM-201 (retifanlimab) and JM200 Part B (avelumab) to estimate the cost-

effectiveness of retifanlimab, with the incremental cost per quality adjusted life year (QALY) gained as the main outcome of the evaluation.

6.38 However, the ESC considered the presented clinical evidence was insufficient to support a claim of superiority for retifanlimab versus avelumab, and therefore the presented cost-utility analysis was not reasonable or informative. The ESC considered that a cost minimisation approach (CMA) would be more reasonable given that the submission's clinical claim of superiority was not adequately supported (paragraph 6.32), and it was plausible that retifanlimab is at least as effective and safe as avelumab in patients with chemotherapy naïve metastatic MCC (paragraph 6.33). The Pre-PBAC response maintained the sponsor's view that clinical evidence supporting the claim of superior effectiveness of retifanlimab over avelumab is of better quality and rigour than that accepted by the PBAC for avelumab in MCC, but indicated 'to ensure timely access to retifanlimab in MCC, the Sponsor is ultimately willing to agree to pricing based on a cost-minimisation analysis (CMA) versus avelumab'.

Cost minimisation approach

6.39 The ESC considered that, for the purposes of the CMA, it was appropriate to assume:

- The average treatment duration for retifanlimab and avelumab were unlikely to be substantially different in clinical practice; and
- Given the uncertainties regarding the average dose for avelumab (see paragraph 6.45), it was reasonable to assume the recommended flat doses in the Product Information documents for both retifanlimab and avelumab.

6.40 The ESC considered the following equi-effective doses would be reasonable: retifanlimab 500 mg every 4 weeks is equi-effective to avelumab 800 mg every 2 weeks. On the basis that the average treatment duration was unlikely to be substantially different, the ESC considered the CMA could be conducted over a 4 week treatment cycle.

6.41 A CMA (based on the published price of avelumab) is presented in Table 9.

Table 9: Cost Minimisation Analysis (CMA) of retifanlimab vs avelumab for advanced MCC, using avelumab published price

	Avelumab	Retifanlimab
Dose	800 mg every 2 weeks (4 vials)	500 mg every 4 weeks (1 vial)
Published price (EMP)	$1,289 per 200 mg vial	$10,438 per 500 mg vial
Drug cost per dose	$5,156	$10,438
Drug cost per 4 weekly cycle	$10,312	$10,438
Admin cost per 4 weekly cycle [a]	$252	$126
Total cost per patient per 4 weekly cycle	$10,564	$10,564

Source: constructed by the secretariat based on the ESC preferred assumptions (as outlined in paragraphs 6.39 and 6.40)
Admin, administration; CMA, cost minimisation analysis; MCC, Merkel Cell Carcinoma
Note: CMA is based on a 4 weekly treatment cycle and assumes that, in clinical practice, there is not likely to be any difference in treatment duration between avelumab and retifanlimab
[a] Assuming $126 per administration.

Cost utility analysis

6.42 The key components of the submission's model, are summarised in Table 10,

Table 10: Summary of model structure, key inputs and rationale

Component	Description	Justification/Comments
Type of analysis	Cost-utility analysis	The ESC considered the approach is not reasonable as the clinical claim of superiority was not adequately supported (see paragraph 6.32).
Outcomes	PFS; OS	
Time horizon	7.5 years versus a median follow-up of: • 35.7 months in POD1UM-201; and • 21.2 months (PFS, DOR) and 54.3 months (OS) in JM200 Part B	The submission claimed it was reasonable to apply a longer time horizon in the current economic evaluation compared to the 5-year time horizon applied in the avelumab 2018 model base case. Given the high level of uncertainty associated with the unanchored indirect comparisons, extrapolation of the study results beyond 5 years will further increase the extent of uncertainty and therefore may not appropriate.
Methods used to generate results	Partitioned survival model	
Health states	PF; PD; Dead	
Cycle length	28 days	The submission claimed this was aligned with the Q2W and Q4W treatment cycles for avelumab and retifanlimab, respectively.
Transition probabilities	Avelumab arm: Trial period: PFS and OS from JM200 Part B. Extrapolation period: Parametric extrapolation (PFS and OS: Generalised gamma).	Using a HR approach for retifanlimab modelling may not be appropriate as the proportional hazard was violated for PFS, and MAIC results were highly uncertain.
	Retifanlimab arm: Trial and extrapolation period: MAIC2 HRs, applied relative to the avelumab arm. No convergence assumed.	
	KM truncation: Gebski Criterion 2 was used in the base case of the economic model, which corresponded to a truncation point at 24 months for PFS, and 60 months for OS for the JM200 Part B KM data.	The economic model was sensitive to the PFS truncation time point because of ToT being equivalent to PFS. When ToT was unlinked from PFS the model was not sensitive to the truncation point.
	ToT: Economic model links ToT to PFS, with all patients alive and PF assumed to remain on treatment. In the base case analysis, it is estimated 20.4% of avelumab patients remain on treatment >2 years. Retifanlimab treatment duration was limited to 2 years.	Mean avelumab ToT may be overestimated. In JM200 Part B, at 54.3 months follow-up, 94% of patients had discontinued treatment (i.e. 6% [7/116] were ongoing). At the equivalent time point in the modelled avelumab arm (54.3 months, 4.53 years), approximately 15% of patients remained on treatment.

Component	Description	Justification/Comments
Utility values	Health state utility values were sourced from Kaufman 2018b: PF:0.8269; PD:0.7415 AE disutilities were derived from Kaufman 2018b and the incidence of TEAEs in POD1UM-201 and JM200 Part B: RETI arm: -0.0621; AVE arm: -0.0971	Utility values derived from JM200 Part A included patients in the 2L setting and therefore may not be directly relevant to the proposed population, and the UK scoring algorithm used may not be applicable to the Australian population. The incidence in AEs was uncertain as there was no comparative safety data between retifanlimab and avelumab. The ESC considered there was likely insufficient evidence to claim that retifanlimab was superior in safety to avelumab (see Paragraph 6.29
Software	Microsoft Excel	.

Source: Table 82, p177 of the submission

AE = adverse event; AVE = avelumab; HR = hazard ratio; JM200 = JAVELIN Merkel 200; MAIC = matched-adjusted indirect comparison; OS = overall survival; PD = progressed disease; PF = progression-free; PFS = progression-free survival; QALY = quality-adjusted life year; RETI = retifanlimab; ToT = time on treatment

6.43 The submission fitted parametric functions to digitised OS and PFS KM data from the JM200 Part B study publications to extrapolate beyond the study follow up, then applied the MAIC2 HRs (Table 7) relative to the avelumab arm to estimate the benefits of retifanlimab treatment compared to the avelumab arm. A constant survival benefit persisting over the 7.5-year time horizon was assumed for patients in the retifanlimab arm relative to the avelumab arm.

6.44 The economic model linked time on treatment (ToT) to PFS, assuming that: all patients alive and progression free (PF) remained on treatment, except that retifanlimab treatment was capped at two years whereas avelumab continued indefinitely. This meant that assuming worse PFS for retifanlimab relative to avelumab improved the ICER and vice versa (see paragraph 6.47).

6.45 The weight based avelumab dosage applied in the model was based on the mean weight and kidney function of the POD1UM-201 chemotherapy-naïve metastatic cohort (n=91). Assuming a mean patient weight of 83.03 kg, it was estimated patients receive an average of 4.7 x 200 mg vials per dose, equating to 932 mg per dose. However, the July 2018 avelumab submission estimated a smaller average dose of 849.2 mg per person for avelumab. The submission claimed that this was because the 849.2 mg per person dose was based on JM200 Part A in the 2L setting for MCC, and that this exposure was not applicable to the current evaluation (1L setting). There was no evidence provided to support the claim that the average dose of avelumab would be different across the 1L and 2L setting. A flat dose of 800 mg is also included in the approved product information for avelumab and specified in the PBS listing of avelumab in metastatic MCC.

6.46 The key drivers of the model are summarised in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained
Time horizon	A time horizon of 7.5 years was applied. There were 0.293 LYs accrued (discounted) in the trial period and 0.475 (0.768-0.293) in the extrapolated period, showing that the majority of LYs gained occurred in the extrapolated period.	High, favours retifanlimab Use of a 5-year time horizon increased the ICER by [redacted]%
ToT	The modelled mean ToT was 1.21 years for retifanlimab, and 1.58 years for avelumab. ToT was a key driver as avelumab is not associated with a maximum treatment duration in metastatic MCC, whereas retifanlimab has a maximum treatment duration of 24 months. As a result, the better PFS was in the avelumab arm, the more drug costs were accrued, whereas these drug costs are capped at two years in the retifanlimab arm.	High, favours retifanlimab. Use of a less optimistic PFS/ToT extrapolation (e.g. Weibull) for the avelumab arm increased the ICER by [redacted]%.
Constant risk assumption	The applied relative treatment effect (OS HR: 0.689, PFS HR: 0.519) was assumed to be constant over the 7.5-year time horizon, which may not be reasonable as all retifanlimab patients discontinue treatment at two years.	High, favours retifanlimab Application of curve convergence (OS and PFS) from 3 to 7.5 years increased the ICER by [redacted]%.
Avelumab average dose	The base case avelumab exposure per dose (932.1 mg) was higher than the average dose per treatment of 849.2 mg previously accepted for avelumab (paragraph 6.41, avelumab PSD, July 2018 PBAC Meeting)	High, favours retifanlimab. Application of the 849.2 mg dosage increased the ICER by [redacted]%.

Source: Compiled during evaluation using information in Tables 132 to 135, pp231 – 233 of the submission and the sensitivity analysis.
HR = hazard ratio; ICER = incremental cost effectiveness ratio; LY = life year; MCC = Merkel cell carcinoma; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PF = progression free; PFS = progression free survival; PSD = public summary document; ToT = time on treatment; QALY = quality adjusted life year.
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*

6.47 The submission's base case mean ToT for avelumab was 579 days (82.4 weeks), and the modelled mean ToT for retifanlimab was 442 days (63.1 weeks). As the retifanlimab ToT was directly proportional to the avelumab ToT (equivalent to PFS, see paragraph 6.43), a shorter median ToT (and PFS) for avelumab was favourable to retifanlimab due to reduced retifanlimab drug costs in the first two years of the model. Conversely, as retifanlimab treatment is capped at two years, a longer mean ToT for avelumab favours retifanlimab, as drug costs for avelumab continue to accrue beyond two years. In addition, mean avelumab ToT was proportional to the selected time horizon due to the long right tail of continuing patients in the PF state. For example, reducing the time horizon to five years reduced the mean avelumab ToT from 1.58 to 1.27 years.

6.48 The results of the stepped economic evaluation for the submission's CUA are summarised in Table 12. A base case incremental cost effectiveness ratio (ICER) of $55,000 to < $75,000 per QALY was estimated for retifanlimab versus avelumab in patients with metastatic MCC.

Table 12: Results of the stepped economic evaluation (based on published price of avelumab)

Step and component	Proposed medicine	Comparator	Increment
Step 1: Trial-based costs and outcomes			
Costs	$[redacted]	$153,571	$[redacted]
PFLY	1.542	0.899	0.643
LYG	2.015	1.722	0.293
Incremental cost/extra LY gained			$[redacted][1]
Step 2: Translation of survival outcomes to QALYs			
Costs	$[redacted]	$153,571	$[redacted]
QALY	1.564	1.257	0.307
LYG	2.015	1.722	0.293
Incremental cost/extra QALY gained			$[redacted][1]
Step 3: Extrapolation of survival outcomes over the 7.5-year time horizon			
Costs	$[redacted]	$231,115	$[redacted]
QALY	2.927	2.201	0.725
LYG	3.707	2.939	0.768
Incremental cost/extra QALY gained			$[redacted][2]
Step 4: Inclusion of other healthcare resource use			
Costs	$[redacted]	$260,076	$[redacted]
QALY	2.927	2.201	0.725
LYG	3.707	2.939	0.768
Incremental cost/extra QALY gained			$[redacted][3]

Source: Table 128, p228 of the submission and 'Results' sheet from the submissions economic model

ICER = incremental cost-effectiveness ratio; LY = life year; PFLY = progression-free life year; QALY = quality-adjusted life year.

The redacted values correspond to the following ranges:

[1] *$455,000 to < $555,000*

[2] *$75,000 to < $95,000*

[3] *$55,000 to < $75,000*

6.49 The results of key univariate and multivariate sensitivity analyses are summarised in Table 13.

Table 13: Results of Key Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	Δ% from base case
Base case	**$[redacted]**	**0.725**	**$[redacted]** [1]	-
Discount rate (base case 5% costs and outcomes)				
• 0%	$[redacted]	0.851	$[redacted] [2]	-[redacted]%
• 3.5%	$[redacted]	0.760	$[redacted] [1]	-[redacted]%
Time horizon (base case 7.5 yrs)				
• 5 yrs	$[redacted]	0.505	$[redacted] [3]	[redacted]%
Relative treatment effects (base case: MAIC 2, OS HR: 0.689, PFS HR: 0.519)				
• MAIC 1 (OS HR: 0.80)	$[redacted]	0.504	$[redacted] [4]	[redacted]%
• MAIC 1 (PFS HR: 0.59) ToT linked [a]	$[redacted]	0.701	$[redacted] [5]	-[redacted]%
• MAIC 1 (PFS HR: 0.59) ToT unlinked [a]	$[redacted]	0.701	$[redacted] [6]	[redacted]%
PFS parametric model (base case: Gen.gamma)				
• Weibull (ToT linked)	$[redacted]	0.716	$[redacted] [7]	[redacted]%
• Loglogistic (ToT linked)	$[redacted]	0.722	$[redacted] [4]	[redacted]%
• Lognormal (ToT linked)	$[redacted]	0.721	$[redacted] [4]	[redacted]%
Extrapolation assumptions (base case: no convergence)				
• Risk convergence from 3 yrs [b]	$[redacted]	0.628	$[redacted] [6]	[redacted]%
• Risk convergence 5 yrs [b]	$[redacted]	0.708	$[redacted] [6]	[redacted]%
• Curve convergence between 3[c] and 7.5 yrs	$[redacted]	0.510	$[redacted] [4]	[redacted]%
• Curve convergence between 5[c] and 7.5 yrs	$[redacted]	0.610	$[redacted] [6]	[redacted]%
Avelumab exposure per dose (base case: 10 mg/kg including wastage; 932.1 mg)				
• 800 mg flat dosing	$[redacted]	0.725	$[redacted] [7]	[redacted]%
• July 2018 avelumab dose (849.2 mg) [d]	$[redacted]	0.725	$[redacted] [4]	[redacted]%
Duration of KM data (base case: Gebski criterion 2; OS:60 mths, PFS: 24 mths)				
• Gebski criterion 1 (2.5%) (OS: 54 mths, PFS: 18 mths)	$[redacted]	0.727	$[redacted] [1]	-[redacted]%
• Gebski criterion 1 (5%) (OS: 60 mths, PFS: 22 mths)	$[redacted]	0.725	$[redacted] [6]	[redacted]%
Terminal care (base case: $21,005.89 per death)				
• No terminal care costs ($0)	$[redacted]	0.725	$[redacted] [6]	[redacted]%

Source: Tables 132 to 135, pp231 – 233 of the submission

CFB = change from baseline; Gen., generalised; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; yrs, years.

Note: Italicised text reflects sensitivity calculations added during evaluation.

[a] as in the base case, PFS = ToT, therefore, changes to the PFS relative treatment effect directly impact ToT. 'Linked' analyses were conducted with the base case model operation. 'Unlinked' analyses assumed that ToT values were always equal to the base case PFS, allowing PFS to be changed without affecting ToT.

[b] OS and PFS HR after this point assumed to be 1.0

[c] OS and PFS assumed to be equal between arms at 7.5 years, starting at 3 or 5 years as indicated

[d] Based on an average of 4.246 vials (849.2 / 200 mg).

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*

[2] *$35,000 to < $45,000*

[3] *$155,000 to < $255,000*

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

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

[6] *$75,000 to < $95,000*

[7] *$115,000 to < $135,000*

Drug cost/patient/course - $[redacted] per patient per course

Table 14: Drug cost per patient for proposed and comparator drugs

	Retifanlimab			Avelumab		
	Trial dose and duration	**Model**	**Financial estimates**	**Trial dose and duration**	**Model**	**Financial estimates**
Mean dose	500 mg	500 mg	500 mg	NR [c]	932 mg	932 mg
Mean no. doses	13.5	15.8	15.8	NR	41.3	41.3
Mean duration	1.04 years [a]	1.21 years [b]	1.21 years [b]	NR	1.58 years	1.58 years
AEMP per vial (published)	$[redacted]	$[redacted]	$[redacted]	$1,289	$1,289	$1,289
Cost/patient/dose	$[redacted]	$[redacted]	$[redacted]	$5,652 [d]	$6,192 [e]	$6,192 [e]
Cost/patient/course	$[redacted] [a]	$[redacted] [f]	$[redacted] [g]	-	$256,024 [f]	$255,730 [g]

Source: Constructed during evaluation from Table 7 POD1UM-201 CSR, Table 130, p230 of the submission, 'Inputs' sheet of the economic model.

AEMP = approved ex manufacturer price

[a] POD1UM-201 reported 13.5 mean total number of infusions. Assuming no treatment breaks, 13.5 x Q4W = 54 weeks. 13.5 x the cost per dose = the total cost per course. No patients remained on treatment.

[b] Based on the assumption that time on treatment was the same as progression free survival for retifanlimab

[c] The July 2018 avelumab submission estimated an average dose per treatment of 849.2 mg per person for avelumab based on JM200 Part A in the 2L setting for MCC. Avelumab is PBS listed and TGA approved for both 800 mg (flat) and 10 mg/kg dosing

[d] Based on the 849.2 mg mean dosage applied in the July 2018 Avelumab submission, equivalent to 4.246 vials. This was imputed in Cell C82 of 'Inputs' in the submissions economic model, with doses per cycle set to 1.0.

[e] Doses per cycle (Cell C87 , 'Inputs') set to 1.0 to calculate the cost per Q2W cycle of avelumab. The same DPMA assumptions were applied in the submission's financial estimates (i.e. PBS fees and markups, and 29.7% public/private split).

[f] Undiscounted drug costs from 'Results' sheet of the economic model.

[g] mean no. doses x cost/patient/dose

6.50 Drug cost/patient/course was calculated using the published price for avelumab ($1,289.49), and the placeholder effective price for retifanlimab applied in submission's economic model ($[redacted] per dose, public/private split 29.7%). The cost/patient/dose was inclusive of PBS fees and mark-ups for Efficient Funding of Chemotherapy items.

6.51 There were minor differences in the undiscounted drug costs from the submission's economic model and the cost/patient/course assumptions applied in the financial estimates. The evaluation considered that this difference appeared to be due to rounding error in the economic model, which may be attributed to the 28-day cycle length.

Estimated PBS usage & financial implications

6.52 This submission was considered by DUSC.

6.53 A mixed model approach was used for estimating the financial implications associated with the PBS listing of retifanlimab in the requested PBS population. This approach was primarily a market share approach based on the historical script numbers of avelumab, with future usage estimated by linear extrapolation.

6.54 Estimated substituted avelumab scripts were translated into retifanlimab scripts via a script substitution rate. The script substitution rate between retifanlimab and

avelumab was estimated based on modelled ToT in the economic model (ie linked to PFS). A ToT of 1.21 years for retifanlimab, equating to 15.8 scripts, and 1.58 years for avelumab, equating to 41.3 scripts, resulted in a substitution rate of 38.26% (41.3/15.8). The script substitution rate was dependent on modelled ToT, and thus uncertain, with mean avelumab ToT potentially overestimated (see paragraph 6.47).

6.55 A summary of data sources and parameter values applied in the analysis is provided in Table 15.

Table 15: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Incident patients	Not provided.	NA	The interpretability of the retifanlimab budget impact model was limited without patient counts. The number of incident patients was estimated based on avelumab scripts on the PBS during the evaluation. DUSC agreed with the approach used by the sponsor and its use of a market share method.
Prevalent patients	Not provided.	NA	
Projected service use of avelumab without retifanlimab listing	*Total services* Yr 1 (2026): 5,746 Yr 2 (2027): 6,179 Yr 3 (2028): 6,612 Yr 4 (2029): 7,045 Yr 5 (2030): 7,478 Yr 6 (2031): 7,911	PBS/RPBS services between 2020 and 2024. Assuming linear market growth of initiating and continuing scripts continues over the analysis period (2026-2031).	Using script numbers instead of underlying patient numbers may increase uncertainty as average utilisation of avelumab was uncertain. DUSC noted current trends of avelumab utilisation and considered this to be reasonable.
Recurrent locally advanced not amenable to surgery or RT	15%	Assumption	Uncertain as not based on any evidence. Used to validate the usage of retifanlimab in expanded population of Recurrent locally advanced not amenable to surgery or RT. DUSC considered this to be uncertain but likely reasonable. DUSC noted the POD1UM-201 trial reported this input to be 9.9% and considered it would likely be lower in the real-world setting.
Market Growth Assumptions			
Uptake rate	Assumed the total immunotherapy uptake rate would increase by [redacted]% (i.e. from [redacted]% to [redacted]%) due to additional uptake of retifanlimab in metastatic MCC.	Assumption	Likely overestimated, as these patients would have been eligible for avelumab but opted not to use immunotherapy. DUSC noted a White Paper released by IQVIA in 2022[12] which indicated that new listings shift market share rather than expand uptake.

[12] IQVIA. (2022, May 9). In the eye of the storm: PD-(L)1 inhibitors weathering turbulence. IQVIA. https://www.iqvia.com/library/white-papers/in-the-eye-of-the-storm-pd-l-1-inhibitors-weathering-turbulence

Data	Value	Source	Comment
Expanded population	11% due to expanded population in recurrent, advanced locoregional MCC	In POD1UM-201, 9.9% (10/101) of chemotherapy-naïve patients had advanced disease compared to 89.1% with metastatic disease. The current immunotherapy MCC market was therefore increased by 11.0% [i.e., 9.9%/(1-9.9%)]	It was unclear whether the relative distribution of recurrent, advanced to metastatic MCC in POD1UM-201 was representative of the Australian population. DUSC considered the POD1UM-201 trial to be the most appropriate source despite likely not being the most accurate representation of the Australian population.
Treatment Utilisation			
Substitution rate (retifanlimab replacing avelumab)	Initiation 2026 = [redacted]%, 2027 – 2031: [redacted]% Continuing 2026 = [redacted]%, 2027 = [redacted]%, 2028 - 2031 = [redacted]%	Assumption	The submission did not justify the applied substitution rates. It was unclear if a [redacted]% substitution rate (instead of [redacted]%) was consistent with the claim of superior clinical efficacy for retifanlimab versus avelumab. For the initiating population DUSC considered it to be reasonable as it is unlikely to claim the entire market given uncertain clinical claim however the dosage schedule would be more appealing. For the continuing population DUSC considered it unlikely many patients would move to retifanlimab if already tolerating avelumab.
Time on treatment (ToT)	1.58 years (avelumab) Equivalent to 41.3 mean scripts per treatment. 1.21 years (retifanlimab) Equivalent to 15.8 mean scripts per treatment.	Modelled mean ToT.	The mean ToT for both medicines was uncertain.
Compliance	100%	Assumed	This was consistent with the economic model; however treatment breaks may be expected in clinical practice. DUSC considered this to be reasonable however noted that it would be lower in clinical practice at approximately 90-95%.
Script substitution rate	38.26% (converting avelumab script counts to retifanlimab scripts)	A ToT of 1.21 years for retifanlimab, equating to 15.8 scripts, and 1.58 years for avelumab, equating to 41.3 scripts, resulting in a substitution rate of 38.26% (41.3/15.8).	The substitution rate was derived from the ToT for both retifanlimab and avelumab, and therefore uncertain.

Data	Value	Source	Comment
Scripts dispensed	Total projected retifanlimab script use Yr 1 (2026): [redacted][1] Yr 2 (2027): [redacted][1] Yr 3 (2028): [redacted][1] Yr 4 (2029): [redacted][1] Yr 5 (2030): [redacted][1] Yr 6 (2031): [redacted][1]	• Substitution of avelumab scripts; plus • additional uptake of immunotherapies scripts; plus • expanded population scripts.	Given uncertainty with the script substitution rate and lack of information around how many patients are actually being treated, this should be considered highly uncertain and may not be consistent with actual patient numbers
Costs			
Retifanlimab	AEMP = $22,000.00 (published) DPMQ (public): $22,091.23; DPMQ (private): $22,444.90	Requested published price.	
Avelumab	AEMP = $1,289.49 per 200 mg vial (published) Adjusted AEMP = $6,009.57 per 932.1 mg DPMQ (public): $6,100.80 DPMQ (private): $6,230.60	Published price. Assuming a mean patient weight of 83.03 kg, it was estimated patients receive an average of 4.7 x 200 mg vials per dose, equating to 932.1 mg per dose. This results in an adjusted AEMP price per dose of $6,009.57.	The dosages used may not be appropriate and higher than previous considerations by the PBAC. Additionally, subsequent to PBS listing of avelumab for MCC, a flat 800mg dose of avelumab was recommended in the TGA approved PI. DUSC noted the updated dosage distribution of avelumab based on PBS dispensing data indicates that the mean dose was 829 mg.
MBS costs	Administration fee $126.00	MBS item 13950	

Source: Compiled during evaluation from Table 137, Table 139, Table 145, Table 152 and Table 153 of the submission
Abbreviations: AEMP = Approved Ex-Manufacturer Price; CIC = committee in confidence; DPMQ = Dispensed Price for Maximum Quantity; NA = not applicable; MBS = Medicare Benefits Scheme; MCC = Merkel cell carcinoma; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; RT = radiation therapy; ToT = time on treatment; Yr = year.
The redacted values correspond to the following ranges:
[1] 500 to < 5,000

6.56 The estimated use and financial implications for the listing of retifanlimab using published prices are presented in Table 16.

Table 16: Estimated use and financial implications (published)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use (scripts)						
Substitution of avelumab	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Additional uptake (+[redacted]%) of immunotherapies	[redacted][2]	[redacted][2]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Expanded population (+11%)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total retifanlimab scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of retifanlimab						
Cost to PBS/RPBS less copayments	$[redacted][3]	$[redacted][4]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][7]
Estimated financial implications for avelumab						
Cost to PBS/RPBS less copayments	-$[redacted][8]	-$[redacted][9]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net financial implications for the health budget						
Net cost to PBS/RPBS	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to MBS	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]
Net cost to PBS/RPBS/MBS	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][3]	$[redacted][3]	$[redacted][3]

Source: Table 167, p258 of the submission

Abbreviations: MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *< 500*

[3] *$30 million to < $40 million*

[4] *$40 million to < $50 million*

[5] *$50 million to < $60 million*

[6] *$60 million to < $70 million*

[7] *$70 million to < $80 million*

[8] *$10 million to < $20 million*

[9] *$20 million to < $30 million*

[10] *$0 to < $10 million*

6.57 Table 17 compares actual utilisation data for avelumab in MCC with the submission's extracted historical PBS services and linear projected services.

Table 17: Merkel Cell Carcinoma avelumab utilisation estimates, 2019 - 2031

	Actual utilisation			Submission estimates		
Year	Prevalent patients	Initiating patients	Scripts	Total projected avelumab scripts	Initiating projected avelumab scripts	Back-calculated initiating avelumab patients [a]
2019	182	182	1,856	1,618	1,127	125
2020	235	113	3,082	3,055	1,135	126
2021	268	136	3,631	3,649	1,242	138
2022	321	147	4,402	4,426	1,345	149
2023	344	147	4,405	4,329	1,199	133
2024	347	155	4,853	4,880	1,561	173
2025[b]	298[b]	89	2,802	5,313	1,642	182
2026	-	-	-	5,746	1,723	191
2027	-	-	-	6,179	1,804	200
2028	-	-	-	6,612	1,885	209
2029	-	-	-	7,045	1,966	218
2030	-	-	-	7,478	2,047	227
2031	-	-	-	7,911	2,128	236

Source: DUSC related documents, 'Avelumab MCC Epi' – Utilisation data current to 28th July 2025, provided by DUSC Secretariat; and the submission's budget impact model.

Notes: The submission claimed projected avelumab scripts were based on PBS use between 2020-2024.

[a] Initiating projected avelumab scripts divided by 9 (maximum numbers of avelumab initial doses). Note that these back-calculated values reflect the minimum number of patients, as it assumes 100% compliance.

[b] to 31 July 2025

6.58 The evaluation considered that the net financial impact to the PBS/RPBS for the listing of retifanlimab was also potentially underestimated, as:

- The script substitution rate was dependent on modelled ToT, which was uncertain and potentially overestimated (see paragraph 6.47).;
- The mean avelumab dosage in the base case (932.1 mg) was higher than the accepted mean dosage at the July 2018 PBAC meeting (849.2 mg), which may overestimate avelumab offset costs.; and
- It was unclear whether a substitution rate of 75% for retifanlimab over avelumab was reasonable, given the claim of clinical superiority. Should clinical superiority and superior safety be accepted, the substitution rate may be higher for the newly listed treatment.

6.59 However, the evaluation considered that the net financial impact could be potentially overestimated, as:

- The market growth assumption of additional immunotherapy uptake (base case +[redacted]%) was likely to be overestimated, as eligible patients would be expected to have initiated avelumab treatment. Given that both avelumab and retifanlimab are PD-1/PD-L1 inhibitors, it was unlikely there would be additional patients opting to receive retifanlimab, as they would have been eligible to initiate avelumab. DUSC considered that the uptake rates applied and the implication that the listing of retifanlimab will grow the immunotherapy market is unlikely to occur in practice and should be amended; and

- The implied number of patients initiating avelumab treatment in the submission's estimates may be overestimated when compared to the actual number of patients who initiated treatment. In 2024, 155 patients initiated avelumab treatment, whereas the submission's input of 1,561 initiating scripts was equivalent to at least 173 initiating patients (calculated by dividing number of initiating scripts by 9, the maximum number of scripts allowed under the PBS listing for initiating avelumab). An overestimate in the most recent data point likely had a disproportionately large effect on the linear extrapolation compared to overestimations in the earlier data points and likely to have led to an overestimate in avelumab utilisation. Given the use of a market share approach, this suggests that the growth of avelumab and therefore the financial estimates may be overestimated.

6.60 Overall, the evaluation considered that the submission's budget impact model was uncertain due to:

- uncertainty around assumptions of avelumab utilisation (both duration and dose), which is pivotal to the estimates and underpins the substitution rate;
- the assumed market growth and proportion of recurrent locally advanced MCC patients treated was uncertain; and
- without an accurate estimate of patient numbers, the uncertainty with avelumab usage cannot be disentangled from retifanlimab uptake and utilisation.

Financial Management – Risk Sharing Arrangements

6.61 The submission stated the Sponsor would be willing to negotiate entering into a risk sharing arrangement (RSA) for retifanlimab in MCC, however no further detail was provided. The submission claimed that as treatment with retifanlimab is limited to a maximum of 24 months, it may be reasonable for retifanlimab listing to occur without an RSA.

6.62 The evaluation considered that given the uncertainty associated with the size of the expanded population and treatment uptake for retifanlimab, the inclusion of a RSA may be prudent. The PBAC previously considered that for avelumab in metastatic MCC a RSA would be required to manage uncertainties around the uptake rates and time on treatment (paragraph 7.17, avelumab PSD, July 2018 PBAC Meeting).

6.63 The ESC considered that it would be appropriate for retifanlimab to join the avelumab RSA.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the listing of retifanlimab for the treatment of metastatic or recurrent, locally advanced Merkel cell carcinoma (MCC) not amenable to curative surgery or radiation. The PBAC was of a mind to recommend retifanlimab pending the provision of a positive TGA Delegate's Overview. The PBAC

did not accept the clinical claim of superiority (in terms of effectiveness and safety) versus avelumab, but accepted that retifanlimab was likely to be non-inferior to avelumab for MCC. The PBAC considered retifanlimab would be cost effective with the same cost per 4 weekly treatment cycle as avelumab. The PBAC noted there was some uncertainty regarding the treatment duration of retifanlimab and avelumab but considered that there was unlikely to be a substantial difference in clinical practice.

7.2 The PBAC considered there is a small unmet clinical need for the first line treatment of metastatic MCC, noting there are currently other treatment options including avelumab and chemotherapy. The PBAC noted that the listing of retifanlimab may improve access for rural and regional patients given its less frequent and faster administration compared with avelumab. The PBAC considered that there is a greater unmet need for recurrent, locally advanced MCC not amenable to surgery or radiation, as there are currently no PBS-listed immunotherapies and patients are limited to standard of care (SoC) chemotherapy, although acknowledged the potential overlap of this population with the metastatic population.

7.3 The PBAC welcomed input from individuals, health care professionals and organisations, which noted that MCC is a rare and aggressive neuroendocrine tumour, and described potential benefits associated with retifanlimab including less frequent dosing (every 4 weeks, Q4W), and a faster infusion rate (30 minutes), compared to avelumab (dosing every 2 weeks, Q2W and 60 minute infusion).

7.4 With regards to the restriction criteria, the PBAC advised the following:

- A combined initial and continuing (STREAMLINED) restriction was appropriate;
- It should include recurrent locally advanced MCC not amenable to surgery or radiotherapy, as per the proposed TGA Product information (PI) (paragraph 3.4).
- It was appropriate to specify that no increase in the maximum amount or number of units may be authorised (paragraph 3.3);
- Omission of ECOG performance status was reasonable (paragraph 3.5);
- The restriction should not allow treatment switching between Programmed Death 1/Ligand-1 (PD-(L)1) inhibitor therapies e.g. for reasons of intolerance, progression or convenience (paragraph 3.6).
- The clinical criterion 'Patient must be untreated with programmed cell death-1/ligand 1 (PD-1/PD-L1) inhibitor therapy at initiation therapy for this indication' will ensure once per lifetime access to immunotherapy for MCC. This should be flowed on to the avelumab listing.

7.5 The PBAC considered that the submission's nominated comparator of avelumab, was appropriate for the metastatic population. The PBAC noted that the submission nominated SoC chemotherapy as the comparator for the locally advanced MCC population as patients are not eligible for avelumab under the existing restriction,

however a clinical comparison was not presented in the submission. The PBAC agreed with the ESC that this population was relatively small, and there was overlap with the metastatic population, hence accepted avelumab as the single comparator for retifanlimab.

7.6 The submission was based on two single arm, Phase 2 studies of: retifanlimab (POD1UM-201, N=107); and avelumab (JM200 Part B, N=116) in adults with MCC (see paragraph 6.4), which formed the basis of two unanchored matched adjusted indirect comparisons (MAICs), of retifanlimab versus avelumab in metastatic MCC on the outcomes of overall survival (OS), progression free survival (PFS) and objective response rate (ORR) (paragraph 6.8), and an unadjusted unanchored indirect comparison on safety outcomes.

7.7 The PBAC noted that although the point estimates for the hazard ratios (HRs) for OS from the MAICs favoured retifanlimab, the differences were not statistically significant (MAIC1: 0.80, 95% CI 0.49, 1.30. MAIC2: 0.689, 95% CI 0.405 to 1.172). The PBAC noted the estimated differences in PFS statistically favoured retifanlimab (MAIC 1: 0.590, 95% CI 0.396 to 0.881. MAIC 2: 0.519, 95% CI 0.343 to 0.786). However, the PBAC considered the results to be subject to a high degree of uncertainty due to low effective sample size, differences in follow-up between studies, and likely unsupported assumptions regarding treatment effect modification for race and ethnicity (specifically in MAIC 2. See paragraphs 6.18 - 6.21). Overall, the PBAC agreed with the ESC that the available evidence was insufficient to support the claim that retifanlimab was superior to avelumab. However, the PBAC accepted that it is plausible that retifanlimab is non-inferior to avelumab on the basis of the MAIC presented in the submission and the published population-adjusted indirect comparison (PAIC) by Kearney 2025, as well as their similar mechanisms of action.

7.8 The PBAC considered that the indirect comparison of the safety of retifanlimab and avelumab was difficult to interpret and at risk of confounding due to the single arm, open-label design which limited the assessment of adverse events (AEs) as the incremental safety associated with retifanlimab and avelumab could not be derived, and differences in patient baseline characteristics. Notably, patients enrolled in POD1UM-201 were younger and potentially healthier (i.e. in terms of ECOG scores and disease severity) on average than those enrolled in JM200 Part B. However, the PBAC considered that the claim of superior comparative safety was not adequately supported by the data, but that it was reasonable to assume non-inferior safety given that retifanlimab and avelumab are both PD-(L)1 inhibitors and are expected to have a broadly similar safety profile.

7.9 The PBAC considered that a cost minimisation approach (CMA) was appropriate, given its view that retifanlimab is non-inferior to avelumab. The PBAC considered it is reasonable to assume that retifanlimab 500 mg every 4 weeks is equi-effective to avelumab 800 mg every 2 weeks based on the flat dosing regimens recommended in their respective PIs, noting the uncertainties associated with weight-based dosing regimens. The PBAC considered that the average treatment duration for retifanlimab

and avelumab were unlikely to be substantially different in clinical practice, and therefore it was reasonable to conduct the CMA over a 4 weekly treatment cycle (paragraph 6.40).

7.10 The PBAC considered that there would be minimal financial impact associated with the listing of retifanlimab given the CMA proposed as a basis for listing, and that market growth from additional immunotherapy uptake is not expected (paragraph 6.59). The PBAC noted that the DUSC estimated that the proportion of patients with recurrent locally advanced not amenable to surgery or radiotherapy (i.e. not currently eligible for avelumab) would be less than 10% of the current scripts, but considered there would be overlap in the advanced and metastatic populations such that the additional use would be less.

7.11 The PBAC considered that it would be appropriate for retifanlimab to join the existing Risk Sharing Agreement (RSA) for MCC with a small increase in expenditure caps to account for the additional use in patients with recurrent locally advanced disease not amenable to surgery or radiotherapy.

7.12 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:
Deferred

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

The sponsor had no comment.