5.11 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 Section 100 (Efficient Funding of Chemotherapy), Authority Required (STREAMLINED) listing for retifanlimab for use in combination with carboplatin and paclitaxel (CP) for the treatment of inoperable locally recurrent or metastatic squamous cell anal carcinoma (SCAC) not previously treated with systemic chemotherapy.

1.2 Listing was requested on the basis of a cost-effectiveness analysis for retifanlimab + CP versus placebo + CP (or CP alone).

1.3 A summary of the key components of the clinical issue addressed by the submission is presented in Table 1.

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

Component	Description
Population	Adults who have inoperable locally recurrent or metastatic SCAC not previously treated with systemic chemotherapy.
Intervention	Patients receive retifanlimab (up to 12 months or 13 x 28 day cycles) in combination with carboplatin and paclitaxel (up to 6 months or 6 x 28 day cycles) until disease progression or unacceptable toxicity.
Comparator	Carboplatin and paclitaxel (up to 6 months).
Outcomes	Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), duration of response (DOR), disease control rate (DCR), patient-reported outcomes (PROs), safety.
Clinical claim	In patients with inoperable locally recurrent or metastatic SCAC not previously treated with systemic chemotherapy, retifanlimab in combination with carboplatin and paclitaxel is superior in terms of efficacy and inferior in terms of safety when compared to carboplatin and paclitaxel.

Source: Table 1, p8 of the submission.
SCAC = squamous cell anal carcinoma

2 Background

Registration status

2.1 The submission was lodged under the Therapeutic Goods Administration (TGA)/PBAC Parallel Process, to be conducted under the Project ORBIS (Type B) program. The submission stated that the Delegate's Overview was expected on 3 March 2026.

2.2 The proposed TGA indication relevant to this submission was "retifanlimab in combination with carboplatin and paclitaxel for the first-line (1L) treatment of adult patients with metastatic or with inoperable locally recurrent SCAC". Additional TGA indications have been proposed for retifanlimab monotherapy for the second-line (2L) treatment of adult patients with locally recurrent or with metastatic SCAC who have

progressed on or who are intolerant of platinum-based chemotherapy, and for the treatment of adult patients with metastatic or recurrent locally advanced Merkel Cell Carcinoma (MCC).

2.3 The TGA Clinical Evaluation Report (CER) – Round 1 was received in November 2025, indicating that the Clinical Evaluator had no objection to approval of retifanlimab for the indication requested in this submission (i.e. 1L SCAC in combination with carboplatin and paclitaxel) or for the requested MCC indication, however the TGA clinical evaluator recommended that the application for second line treatment of SCAC as a single agent should be rejected (p55, CER – Round 1).

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Amount	Max. amount	№.of Rpts
Retifanlimab 25mg/mL, 20mL vial	Published: Public - $22,091.23 Private - $22,444.90 Effective: Public - $[redacted] Private - $[redacted]	500 mg	5
Available brands			
Zynyz Retifanlimab 500 mg solution concentrate for I.V. infusion, 20 mL vial			

Source: Table 10, p36 of the submission.

3.1 The restriction proposed in the submission is outlined below. The PBAC's suggested additions are in italics and deletions are in strikethrough.

Restriction Summary NEW1 / Treatment of Concept: NEW1A
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 or Stage IV (metastatic)*
Condition: Squamous cell anal cancer
Indication: ~~Inoperable~~ locally recurrent or metastatic squamous cell anal cancer
Treatment Phase: ~~First-line therapy~~
Clinical criteria:
The condition must be inoperable
AND
Clinical criteria:
Treatment must be ~~initiated~~ in combination with *each of, (i)* carboplatin ~~and~~ *(ii)* paclitaxel *at initiation*
AND
Clinical criteria:
Patients must *not* have received ~~no~~ prior systemic *anti-cancer* therapy *in the inoperable locally recurrent/metastatic setting at the time treatment with this drug is initiated for this condition*
AND
Clinical criteria:
Patient must not have experienced disease recurrence or progression while being treated with this drug for this condition
AND
Clinical criteria:
The treatment must not exceed *a total of (i) cumulative* 12 months; *(ii) 13 doses of this drug whichever comes first from the first dose of this drug regardless of whether it was PBS/non-PBS subsidised*

Source: Table 11, p38 of the submission.
Italics = additions proposed by the secretariat
~~Strikethrough~~ = deletions proposed by the secretariat

3.2 The submission requested a Special Pricing Arrangement, with a proposed effective ex-manufacturer price of $[redacted] per 500 mg vial. In the pre-PBAC response, this was reduced to $[redacted].

3.3 The proposed restriction stated that retifanlimab treatment must be initiated in combination with CP, which was consistent with POD1UM-303, where all patients received at least one dose of carboplatin and one dose of paclitaxel[1]. While the proposed restriction states that retifanlimab "must be initiated in combination with" CP, the draft product information (PI) states that retifanlimab must be used "in combination with" CP, and in the POD1UM-303 trial patients received CP for 6 months.

[1] Number of doses in the retifanlimab + CP arm (mean, median, range): carboplatin = 5.2 infusions, 6.0 infusions, 1-6 infusions; paclitaxel = 13.4 infusions, 15.0 infusions, 1-18 infusions. Number of doses in the placebo + CP arm (mean, median, range): carboplatin = 5.0 infusions, 6.0 infusions, 1-6 infusions; paclitaxel = 13.4 infusions, 15.0 infusions, 1-18 infusions

3.4 Under the proposed restriction, patients who are contraindicated to carboplatin and/or paclitaxel could not receive retifanlimab. The evaluation considered it would be possible that patients may use one dose of CP only to fulfil the criteria that retifanlimab "must be initiated in combination with" CP, effectively receiving retifanlimab monotherapy, which may not be intended under the proposed restriction, noting that evidence of efficacy for retifanlimab monotherapy was limited, and only for the second-line setting (see paragraph 6.17). However, the ESC considered that it is unlikely the clinicians would cease CP prematurely unless necessary for toxicity, given the best evidence is for combination therapy.

3.5 The ESC considered that the proposed clinical criterion 'Patients must have received no prior systemic therapy' should be amended to 'Patients must not have received prior systemic anti-cancer therapy in the inoperable locally recurrent/metastatic setting at the time treatment with this drug is initiated for this condition'. Further, the ESC considered it was not necessary to include ECOG performance status in the restriction as clinicians are unlikely to prescribe retifanlimab in patients with scores higher than one.

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

4 Population and disease

4.1 Anal cancer is a rare disease that accounts for <1% of all new cancer diagnoses and <3% of all gastrointestinal tumours. SCAC is the dominant histology for anal carcinomas comprising 75%-95% of cases (Pedersen 2025[2]), with an annual incidence of 0.5-2.0 per 100 000 (Rao 2021[3]). SCAC is closely associated with human papilloma virus (HPV), with 86% to 97% of cancers of the anus attributable to HPV infection (National comprehensive Cancer Network (NCCN) anal carcinoma guidelines, version 4.2025[4]). Additionally, people living with human immunodeficiency virus (HIV) have an estimated 37-fold increased risk of being diagnosed with anal cancer compared with the general population (Colón-López 2018[5]).

4.2 Most patients with SCAC present with non-metastatic disease and are commonly considered to be curable with appropriate treatment. The European Society for Medical Oncology (ESMO) anal cancer guidelines (Rao 2021) stated that approximately 10%-20% of patients suffer distant relapse and approximately 10% present with de novo metastatic disease. The NCCN guidelines (version 4.2025)

[2] Pedersen E et al. Incidence and burden of anal cancer - time to fight the growing disparities. ESMO Gastrointestinal Oncology. 2025; Article in Press, 100147. https://doi.org/10.1016/j.esmogo.2025.100147

[3] Rao S et al. Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2021; 32(9): pp1087-1100. https://doi.org/10.1016/j.annonc.2021.06.015

[4] National comprehensive Cancer Network, Clinical Practice Guidelines in Oncology (NCCN Guidelines) Anal Carcinoma, 2025 Version 4. https://www.nccn.org/guidelines/category_1

[5] Colon-Lopez V et al. Anal cancer risk among people with HIV infection in the United States. Journal of Clinical Oncology. 2018; 36(1): pp68-75. https://doi.org/10.1200/JCO.2017.74.9291

stated that patients presenting with distant metastasis have a 30.5% 5-year survival rate.

4.3 The submission proposed use of retifanlimab as 1L treatment in patients with inoperable locally recurrent or metastatic SCAC not previously treated with systemic chemotherapy. Under the proposed listing, there were four populations of patients diagnosed with SCAC who would be eligible for retifanlimab:

- diagnosed with *de novo* metastatic SCAC;
- progress from locoregional to metastatic disease following first-line (1L) conformal radiation therapy (CRT) and/or after surgery;
- progress from locoregional to inoperable locally recurrent disease; and
- progress from operable locally recurrent to metastatic disease after surgery.

4.4 Retifanlimab is a humanised, hinge-stabilised, immunoglobulin (Ig) G4κ monoclonal antibody that binds to human programmed cell death protein 1 (PD-1) receptor. Retifanlimab is designed to restore immune effector function (e.g. T cell activity) by blocking checkpoint inhibitory interactions between PD-1 and its two ligands, PD-L1 and PD-L2.

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

5 Comparator

5.1 For patients with inoperable locally recurrent or metastatic SCAC not previously treated with systemic chemotherapy, the submission nominated CP as the main comparator to retifanlimab + CP. The justifications were that CP is the current standard of care for the 1L treatment of advanced or metastatic SCAC in the NCCN and ESMO guidelines, and that both carboplatin and paclitaxel are subsidised via the PBS (unrestricted benefit). 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'. At that meeting the PBAC recommended a multi-indication (broad) listing for nivolumab and ipilimumab in advanced or metastatic cancers, which would include SCAC, however nivolumab is not currently TGA registered for this indication.

5.2 The evaluation and the ESC considered that the nomination of CP as comparator to retifanlimab + CP was reasonable.

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 health care professionals (17) and organisations (2) including Rare Cancers Australia and MOGA, via the Consumer Comments facility on the PBS website. Comments highlighted the clinical need for new therapies for advanced SCAC, the limited effectiveness of current chemotherapy options, and the challenges of conducting large trials in rare conditions. People living with recurrent/metastatic disease described significant impacts on quality of life, including pain, fatigue, premature menopause, infertility, financial distress, and stigma. Healthcare professionals noted that median survival for SCAC is less than 2 years, and current treatment options are limited to older chemotherapy agents and responses are short-lived. Input described a range of potential benefits of retifanlimab, including improved response rates and disease control.

6.3 The PBAC noted that the Medical Oncology Group of Australia (MOGA) expressed support for the submission. While MOGA noted the results from POD1UM-303, it referred to the POD1UM-202 trial rather than the relevant, POD1UM-303 trial. The PBAC considered it was unclear whether MOGA may have expressed stronger support if the POD1UM-303 trial had been considered.

6.4 The PBAC considered that, based on consumer input, improving response and survival are the most important outcomes for people living with this condition.

Clinical trials

6.5 The submission was based on one head-to-head trial comparing retifanlimab + CP to placebo + CP (N=308), POD1UM-303.

6.6 Details of POD1UM-303 as presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission.

Trial ID	Protocol title/ Publication title	Publication citation
POD1UM-303/ InterAACT 2 (NCT04472429)	A Phase 3 Global, Multicenter, Double-Blind Randomized Study of Carboplatin-Paclitaxel With INCMGA00012 or Placebo in Participants With Inoperable Locally Recurrent or Metastatic Squamous Cell Carcinoma of the Anal Canal Not Previously Treated With Systemic Chemotherapy (POD1UM-303/InterAACT 2)	Clinical Study Report - interim analyses, 15 April 2024
	Rao S, Jones M, Bowman J, Tian C and Spano J-P (2022) POD1UM-303/InterAACT 2: A phase III, global, randomized, double-blind study of retifanlimab or placebo plus carboplatin-paclitaxel in patients with locally advanced or metastatic squamous cell anal carcinoma.	*Front. Oncol*. 12:935383. doi: 10.3389/fonc.2022.935383
	Rao, S., Samalin-Scalzi, E., Evesque, L., Abdelghani, M.B., Morano, F., Roy, A.C., et al. (2025) Retifanlimab with carboplatin and paclitaxel for locally recurrent or metastatic squamous cell carcinoma of the anal canal (POD1UM-303/InterAACT-2): a global, phase 3 randomised controlled trial.	The Lancet 405: 10495. Available at: PIIS0140-6736(25)00631-2
	Rao, S., Samalin-Scalzi, E., Evesque, L., Abdelghani, M.B., Morano, F., Roy, A.C., Dahan, L., Tamberi, S., Dhadda, A.S., Saunders, M.P. and Casanova, N., 2024. LBA2 POD1UM-303/InterAACT 2: phase III study of retifanlimab with carboplatin-paclitaxel (c-p) in patients (Pts) with inoperable locally recurrent or metastatic squamous cell carcinoma of the anal canal (SCAC) not previously treated with systemic chemotherapy (Chemo).	Conference abstract Annals of oncology 35: S1217.

Source: Table 14, p44 of the submission.

6.7 POD1UM-303 was a double-blind trial which compared treatment with retifanlimab + CP with placebo + CP over a maximum treatment duration of one year. After disease progression, patients randomised to placebo + CP could elect to receive open label retifanlimab monotherapy for up to one year. A substantial proportion of patients received anti-cancer treatment subsequent to the discontinuation of study treatment (retifanlimab + CP arm: 53.9%; placebo + CP arm: 42.9%). The key features of the direct randomised trial 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 + CP vs placebo + CP						
POD1UM-303	304	R, DB, MC [a] 12 months [b]	Low (during DB period) [c]	inoperable locally recurrent or metastatic SCAC	PFS, OS	Patient demographics (age, % males, BSA, GFR), PFS and OS KM curves, PF and PD utility values, % serious AEs

Source: Constructed during the evaluation using Section 2.3 of the submission.
AEs = adverse events; BSA = body surface area; CP = carboplatin + paclitaxel; DB = double blind; DCO = data cut-off; GFR = glomerular filtration rate; KM = Kaplan-Meier; MC = multi-centre; OS = overall survival; PD = progressed disease; PF = progression-free; PFS = progression-free survival; R = randomised; SCAC = squamous cell anal carcinoma.
[a] Patients randomised to placebo + CP whose disease progressed were able to then receive open label retifanlimab monotherapy for up to 12 months.
[b] Retifanlimab or placebo treatment (double-blind) could be given for a maximum duration of 13 cycles (12 months). Chemotherapy was given for a maximum of six cycles.
[c] Risk of bias was higher following patient unblinding after disease progression.

6.8 The evaluation considered POD1UM-303 to be at low risk of bias during the double-blind period (retifanlimab + CP vs placebo + CP), but that patient reported outcomes may be at a higher risk of bias following disease progression when patients were unblinded. There may also be potential confounding for overall survival (OS) due to patients randomised to placebo + CP receiving retifanlimab post progression, though this was uncertain (see paragraph 6.16).

Comparative effectiveness

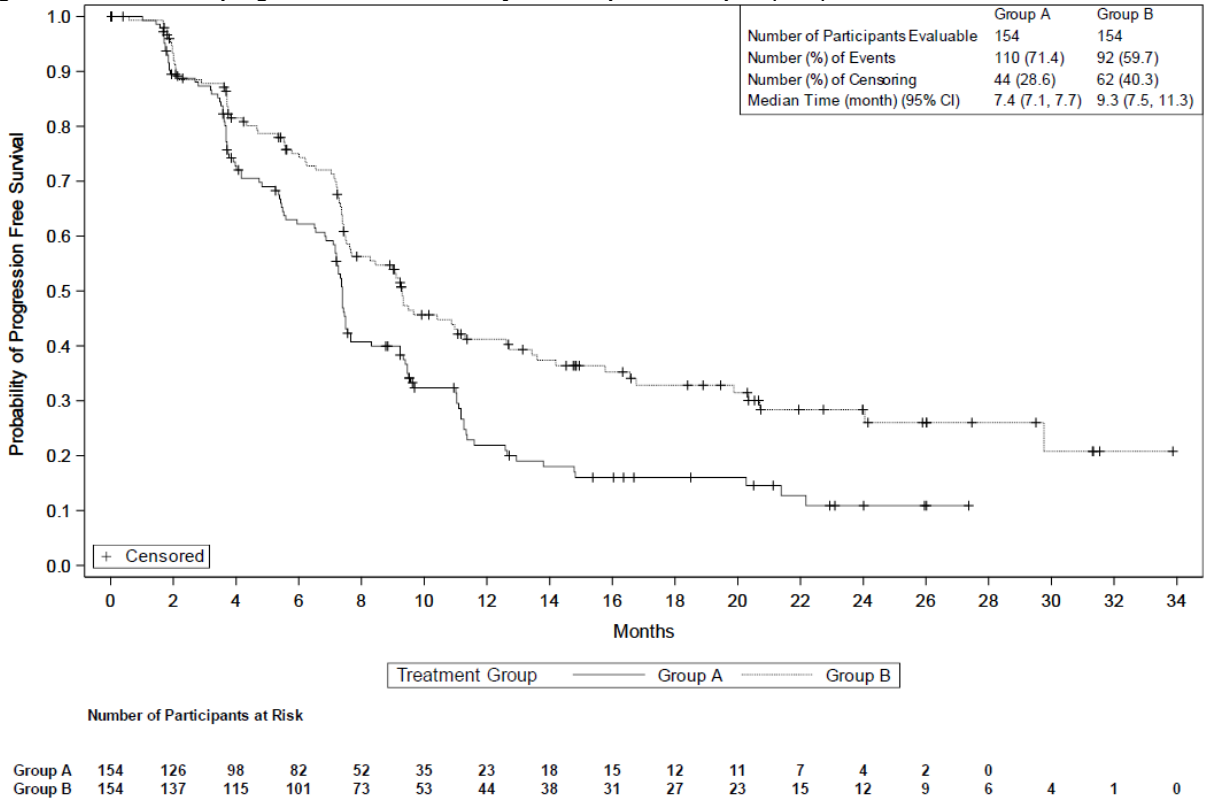
6.9 The POD1UM-303 survival outcome results (progression-free survival [PFS] and OS) at the data cut off (DCO) are summarised in Table 4. The PFS and OS Kaplan-Meier (KM) plots are presented in Figure 1 and Figure 2Figure 2, respectively.

Table 4: Summary of survival outcomes in POD1UM-303 (FAS)

	Retifanlimab + CP (N = 154)	**Placebo + CP (N = 154)**
PFS (primary outcome)		
PFS event, n (%)	92 (59.7)	110 (71.4)
Month 3 PFS rate (95% CI)	87.8 (81.3, 92.1)	87.3 (80.7, 91.8)
Month 6 PFS rate (95% CI)	75.0 (67.1, 81.3)	62.2 (53.5, 69.7)
Month 9 PFS rate (95% CI)	54.0 (45.2, 61.9)	40.0 (31.6, 48.2)
Month 12 PFS rate (95% CI)	41.2 (32.7, 49.6)	21.9 (14.9, 29.7)
Median PFS (months) (95% CI)	9.3 (7.5, 11.3)	7.4 (7.1, 7.7)
PFS (BICR) HR (95% CI); p-value	**0.63 (0.47, 0.84); 0.0006** [a]	
OS (key secondary outcome)		
Median OS (months) (95% CI)	29.2 (24.2, NE)	23.0 (15.1, 27.9)
OS HR (95% CI), p-value	0.70 (0.49, 1.01); 0.0273 [b]	
Other secondary endpoints		
ORR, n (%)	86 (55.8)	68 (44.2)
DCR, n (%)	134 (87.0)	123 (79.9)
DOR, Median (Min, Max)	14.0 (8.6,22.2)	7.2 (5.6,9.3)

Source: Tables 30, 31, 33 and 34, pp72, 74, 78 and 79 of the submission.
BICR = blinded independent central review; CI = confidence interval; CP = chemotherapy (carboplatin + paclitaxel); DCR = disease control rate; DOR = duration of response; FAS = full analysis set; HR = hazard ratio; IPCW = inverse probability of censoring weighting; Min, minimum Max, maximum; NE = not evaluated; ORR = overall response rate; OS =overall survival; PFS = progression-free survival; RPSFT = rank-preserving structural failure time.
Text in **bold** indicated statistically significant difference.
[a] Results from stratified Cox model. Stratification factors included PD-L1 expression (<1% or ≥1%), extent of disease (locally recurrent or metastatic) and region (Australia/Europe/North America/United Kingdom or rest of world).
[b] OS results did not reach statistical significance based on one sided testing at 2.5% (0.025).

Figure 1: POD1UM-303 progression-free survival by BICR Kaplan-Meier plot (FAS)

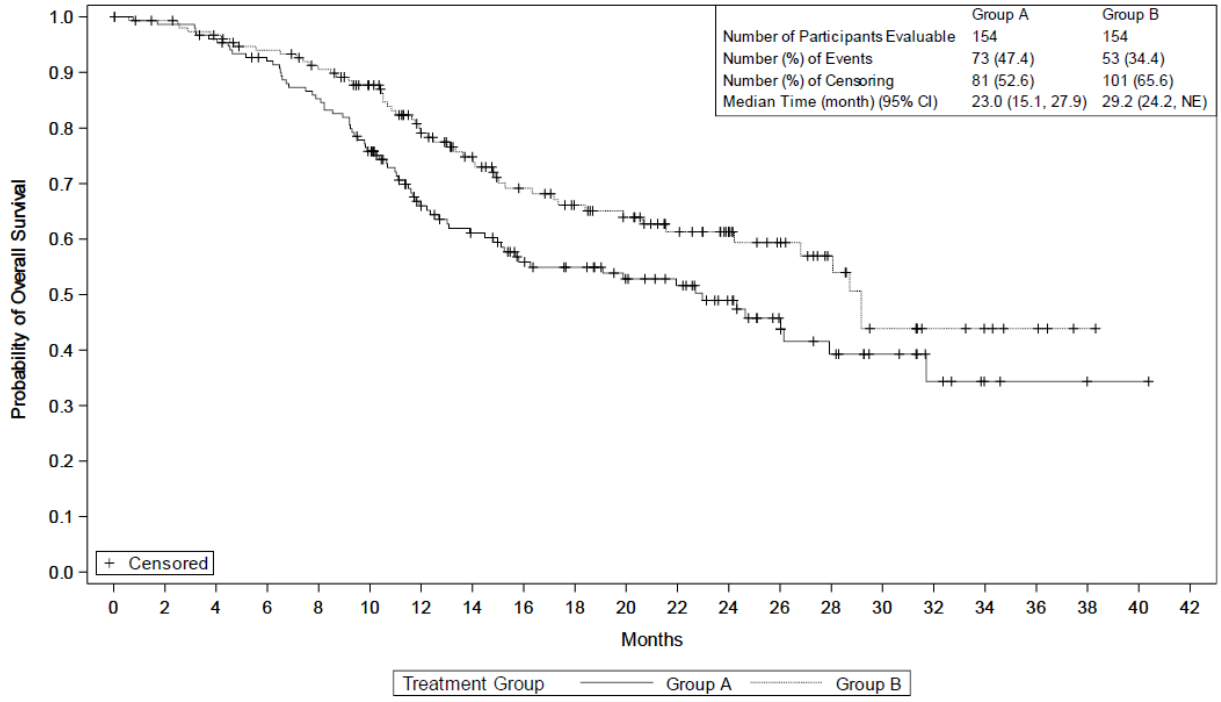


Number of Participants at Risk

Group A	154	126	98	82	52	35	23	18	15	12	11	7	4	2	0		
Group B	154	137	115	101	73	53	44	38	31	27	23	15	12	9	6	4	1	0

Source: Figure 8, p73 of the submission.
BICR = blinded independent central review; CI = confidence interval; FAS = full analysis set
Note: Group A = placebo + chemotherapy, Group B = retifanlimab + placebo

Figure 2: POD1UM-303 overall survival of Kaplan-Meier plot (FAS) – interim analysis



Number of Participants at Risk

Group A	154	150	145	136	126	110	82	73	61	56	48	43	33	23	17	12	7	3	2	1	1	0
Group B	154	151	145	138	130	117	96	82	70	62	56	44	34	27	19	12	8	6	4	1	0	

Source: Figure 9, p75 of the submission.
BICR = blinded independent central review; CI = confidence interval; FAS = full analysis set
Note: Group A = placebo + chemotherapy, Group B = retifanlimab + placebo

6.10 For the POD1UM-303 trial at the DCO, the median PFS in the retifanlimab + CP arm was 9.3 months (95% CI: 7.5, 11.3; median follow-up = 7.57 months) compared to 7.4 months in the placebo + CP arm (95% CI: 7.1, 7.7; median follow-up = 7.13 months). Retifanlimab + CP demonstrated a statistically significant PFS benefit compared to the placebo + CP arm with a 37% reduction in risk of a PFS event (HR = 0.63 [95% CI: 0.47, 0.84]; p = 0.0006). Consequently, the primary endpoint of the study was met.

6.11 At the DCO, 73 (47.4%) patients treated with placebo + CP and 53 (34.4%) patients treated with retifanlimab + CP had died; the ESC noted the OS data were relatively immature. Median OS in the retifanlimab + CP arm was estimated to be 29.2 months (95% CI: 24.2, NE), with a median follow-up time of 14.77 months (range: 0.6-38.3 months), compared to median OS of 23.0 months (95% CI: 15.1, 27.9) for the placebo + CP arm with a follow-up time of 12.86 months (range: 0.0-40.4 months).

6.12 Based on the hierarchical testing design in POD1UM-303, as the null hypothesis for PFS was rejected (because the retifanlimab + CP arm demonstrated a statistically significant PFS benefit compared to the placebo + CP arm at the 1-sided 2.5% level), hypothesis testing for OS could occur. The submission claimed that, despite the relative immaturity of the data, retifanlimab + CP demonstrated a clinically meaningful improvement in OS compared to placebo + CP with a 30% reduction in risk of death (hazard ratio [HR] = 0.70 [95% CI: 0.49, 1.01]; p = 0.0273), and this was reiterated in the Pre-Sub-Committee Response (PSCR). However, the evaluation and the ESC noted that the POD1UM-303 OS results were not considered to be statistically significant at the nominated threshold of 0.025.

6.13 Of the 154 patients randomised to placebo + CP in POD1UM-303, 44.8% (69/154) crossed over to receive retifanlimab monotherapy following disease progression. Of the 106 patients in the placebo + CP arm who experienced progressive disease and were at risk of crossover, 69 (65.1%) crossed over to retifanlimab monotherapy.

6.14 The submission claimed that the POD1UM-303 OS results were likely biased against the retifanlimab + CP arm due to the subsequent use of retifanlimab monotherapy in the placebo + CP arm, thereby resulting in an underestimation of the incremental OS benefit in favour of retifanlimab. Consequently, the submission used the rank-preserving structural failure time (RPSFT) and inverse probability of censoring weighting (IPCW) models to conduct *post hoc* adjustments for treatment switching.

6.15 The POD1UM-303 OS results with and without adjustment for treatment switching are summarised in Table 5.

Table 5: POD1UM-303, OS cross-over adjusted for treatment switching – interim analysis

Variable	Placebo + chemotherapy RPSFT method[a] (N = 154)	Placebo + chemotherapy IPCW method[b] (N = 154)	Placebo + chemotherapy (POD1UM-303 ITT) (n=154)	Retifanlimab + chemotherapy (POD1UM-303 ITT) (N = 154)
Patients with events, n (%)				
Death	73 (47.4)	38 (24.7)	73 (47.4)	53 (34.4)
Censoring	81 (52.6)	116 (75.3)	81 (52.6)	101 (65.6)
Median OS (months) (95% CI)[c]	19.1 (13.4, 27.9)	23.0 (11.5, 27.9)	23.0 (15.1, 27.9)	29.2 (24.2, NE)
Month 12 OS rate (95% CI)	61.7 (53.2, 69.2)	61.2 (44.9, 74.0)	66.0 (57.5, 73.1)	79.1 (71.3, 85.0)
Month 15 OS rate (95% CI)	56.6 (47.8, 64.4)	59.7 (43.7, 72.6)	59.4 (50.6, 67.1)	71.1 (62.3, 78.1)
Month 18 OS rate (95% CI)	52.5 (43.6, 60.7)	56.3 (40.4, 69.5)	54.9 (46.0, 63.0)	66.1 (56.9, 73.8)
Month 24 OS rate (95% CI)	43.6 (33.7, 53.0)	47.5 (28.7, 64.1)	48.9 (39.6, 57.6)	61.3 (51.6, 69.7)
P-value for stratified log-rank test[d]	RPSFT: 0.0055	IPCW: 0.0063	0.0273	
HR from stratified Cox model (95% CI)[e]	0.63 (0.44, 0.90)	0.61 (0.40, 0.95)	0.70 (0.49, 1.01)	
Follow-up time (months)				
Median	11.96	NC	12.86	14.77
Minimum, maximum	0.0, 40.4	NC	0.0, 40.4	0.6, 38.3

Source: Table 47, p99 of the submission, POD1UM-303 CSR Table 16, p. 52
CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IPCW = inverse probability of censoring weighting; NC = not calculated; OS = overall survival; RPSFT = rank-preserving structural failure time
[a] The crossover-adjusted analysis using the RPSFT model followed a naïve multistep approach and did not account for the part of the variation in the counterfactual survival time that arose from the variation in the acceleration factor for patients who crossed over from the placebo group to the treatment group.
[b] The crossover-adjusted analysis employed the IPCW method. Within the probability of censoring (crossover) models, stratification factors, along with age, sex, baseline ECOG status, and baseline sum of diameters from independent assessor were incorporated as baseline covariates. Time-varying covariates included ECOG status, percentage change in the sum of diameters from independent assessors, indicators for disease progression, indicators for the occurrence of new lesions, and indicators for SAEs. Stabilised weights were derived from the probability of censoring models, trimmed at value 10, and incorporated into the weighted stratified log-rank test and the weighted stratified Cox proportional hazards model. Number of deaths considered death in patients who did not crossover, while patients who crossed over were all censored at the time of crossover in this analysis; thus, follow-up time was not calculated.
[c] Median survival time in months was estimated using Kaplan-Meier method. The CI for median survival time was calculated using the method of Brookmeyer and Crowley (1982).
[d] Nominal p-values are provided as summary statistics.
[e] A stratified Cox regression with Efron's method for tie handling was used to estimate the HR.
Note 1: OS was defined as the time in days between date of randomisation and the date of death due to any cause.
Note 2: The number of months was calculated as the number of day(s) divided by 30.4375.
Note 3: Stratification factors were based on information from the Interactive response technology.

6.16 The RPFST model reported an OS HR adjusted for crossover of 0.63 (95% CI 0.44, 0.90; p = 0.0055), while the IPCW model reported an OS HR adjusted for crossover of 0.61 (95% CI 0.40, 0.95; p = 0.0063), which the submission claimed was statistically significant.

6.17 However, the evaluation considered that while crossover post progression may be a confounder, it was unclear whether the *post hoc* crossover-adjusted analyses were reliable:

- Evidence of efficacy for retifanlimab monotherapy in the 2L setting was limited, so treatment benefit could not be established. In POD1UM-202, a single arm open label study of 2L retifanlimab monotherapy (median duration of treatment = 2.8 months [4 infusions], range 0.03-19.4 months) in 94 patients with locally advanced or metastatic SCAC with disease progression on or after platinum-based therapy or who were ineligible for or intolerant to platinum-based chemotherapy, an ORR of just 13.8% (95% CI 7.6%, 22.5%) was reported, compared to 55.8% (95% CI 47.6, 63.8) for retifanlimab + CP in the first line setting in POD1UM-303. Therefore, the evaluation and the ESC considered it may not have been appropriate to conduct the RPSFT analysis, which assumes constant treatment effect.
- The 2L treatment with retifanlimab monotherapy in POD1UM-303 was relatively short (median duration of 1.873 months and median 3.0 doses). The evaluation considered it was uncertain whether this was sufficient to lead to a meaningful difference in OS, as implied by the act of performing crossover adjustments.
- The IPCW model relied on a strong assumption that all prognostic factors at the time of disease progression were accounted for and there were no other unobserved confounders. The evaluation and the ESC considered that this assumption was unlikely to have held, as the decision to use subsequent therapy (or not) was not random. While observable characteristics could be controlled for to a degree statistically, the evaluation and the ESC considered that unobserved variables which contributed to both the decision to use subsequent treatment as well as OS are not accounted for and would undermine the reliability of crossover adjustments, in particular IPCW.

6.18 While the evaluation and the ESC considered it plausible that the addition of an immunotherapy (i.e. retifanlimab) to CP would confer an OS benefit compared to CP alone, the magnitude of this benefit remains uncertain, and it was likely that the crossover adjustment favoured retifanlimab and overestimated the OS benefit associated with retifanlimab + CP compared to CP alone.

6.19 The ESC considered that given the limitations of both IPCW and RPSFT adjustment methods (likely violation of assumptions), the relatively short duration of second-line retifanlimab monotherapy in the trial, and the likely much smaller retifanlimab OS benefit in second-line, the crossover-adjusted analyses were highly uncertain and likely overestimated the benefit of retifanlimab. Overall, the ESC considered the ITT OS results were more informative.

6.20 With regards to other secondary efficacy endpoints in POD1UM-303 (see Table 4):

- The submission (p77) claimed that a "nominally significant improvement" in objective response rate (ORR) was demonstrated for the retifanlimab + CP arm versus the placebo + CP arm (p = 0.0129); 55.8% (95% CI: 47.6, 63.8) compared to 44.2% (95% CI: 36.2, 52.4), respectively. The evaluation noted that given that statistical significance could not be claimed for OS, only nominal P values could be reported for ORR with no Type-1 error allocated for ORR testing;
- The disease control rate (DCR), defined as complete response (CR), partial response (PR) or stable disease (SD), in the retifanlimab + CP arm was 87.0% (95% CI: 80.7, 91.9) compared to the DCR in the placebo + CP arm of 79.9% (95% CI: 72.7, 85.9), based on confirmed responses by blinded independent review committee (BICR); and
- Median duration of response (DOR) was longer for the retifanlimab + CP arm (14.0 months [95% CI: 8.6, 22.2]) compared to the placebo + CP arm (7.2 months [95% CI: 5.6, 9.3]).

Overall, the evaluation considered that ORR, DCR and DOR results were consistent with the primary outcome of PFS favouring retifanlimab + CP compared to placebo + CP in POD1UM-303.

6.21 The health-related quality of life (HRQoL) patient-reported outcomes assessed in POD1UM-303 were EuroQol-5D (EQ-5D), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Anal Cancer module (27 items) (EORTC QLQ-ANL27). Descriptive statistics were used to summarise the scored scales at each scheduled assessment timepoint and change from baseline in the domain scores at the time of each assessment were summarised. No formal statistical tests were provided.

6.22 The evaluation considered that patient reported outcomes were associated with a high risk of responder bias, as not all patients were included in the analysis (e.g. only 186/308 patients had any results for EQ-5D, down to 127/308 at week 24, and 50/308 at the end of treatment). The submission noted difference in mean EORTC QLQ-C30 score of 10.0 favouring the retifanlimab + CP arm, though the reason for this difference was not explained, especially as retifanlimab + CP was associated with more adverse events (AEs) than placebo + CP. EQ-5D results from POD1UM-303 were used to inform the economic model (see paragraph 6.43).

6.23 The submission reported that utilities derived from POD1UM-303 (EQ-5D individual patient data mapped via the validated Australian value set, Norman 2023) were similar between the treatment arms: pre-progression retifanlimab + CP 0.872, placebo + CP 0.873; post-progression retifanlimab + CP 0.750, placebo + CP 0.785.

Comparative harms

6.24 A summary of the overall treatment emergent AEs (TEAEs) in POD1UM-303 is presented in Table 6. Retifanlimab/placebo-related TEAEs, serious retifanlimab/placebo-related TEAEs and retifanlimab/placebo discontinued due to TEAE were all observed more commonly in the retifanlimab + CP arm.

Table 6: POD1UM-303, overall summary of TEAEs during the randomised treatment period (safety population)

Patients (n [%]) with:	Retifanlimab + CP (N = 154)	Placebo + CP (N = 152)	RR (95% CI)	RD (95% CI)
TEAE	154 (100.0%)	152 (100.0%)	1.00 (1.00, 1.00)	0.0 (0.0, 0.0)
Retifanlimab/placebo-related TEAEs	138 (89.6%)	118 (77.6%)	**1.15 (1.04, 1.28)**	**12.0 (3.8, 20.2)**
Serious TEAE	73 (47.4%)	59 (38.8%)	1.22 (0.94, 1.58)	8.6 (-2.5, 19.6)
Grade 3 or higher TEAE	128 (83.1%)	114 (75.0%)	1.11 (0.99, 1.24)	8.1 (-1.0, 17.2)
Fatal TEAE	4 (2.6%)	1 (0.7%)	3.95 (0.45, 34.92)	1.9 (-0.9, 4.8)
Serious retifanlimab/placebo-related TEAE	25 (16.2%)	10 (6.6%)	**2.47 (1.23, 4.96)**	**9.7 (2.6, 16.7)**
Grade 3 or higher retifanlimab/placebo-related TEAE	53 (34.4%)	39 (25.7%)	1.34 (0.95, 1.90)	8.8 (-1.5, 19.0)
Retifanlimab/placebo infusion interruption due to TEAE	6 (3.9%)	2 (1.3%)	2.96 (0.61, 14.44)	2.6 (-1.0, 6.1)
Retifanlimab/placebo dose delayed due to TEAE	81 (52.6%)	75 (49.3%)	1.07 (0.86, 1.33)	3.3 (-7.9, 14.5)
Retifanlimab/placebo discontinued due to TEAE	17 (11.0%)	4 (2.6%)	**4.19 (1.44, 12.18)**	**8.4 (2.8, 14.0)**
Chemotherapy-related TEAE	152 (98.7%)	148 (97.4%)	1.01 (0.98, 1.05)	1.3 (-1.8, 4.4)
Chemotherapy discontinued due to TEAE	16 (10.4%)	8 (5.3%)	1.97 (0.87, 4.48)	5.1 (-0.9, 11.1)
Chemotherapy infusion interruption due to TEAE	18 (11.7%)	18 (11.8%)	0.99 (0.53, 1.82)	-0.2 (-7.4, 7.1)
Chemotherapy dose delayed due to TEAE	107 (69.5%)	108 (71.1%)	0.98 (0.85, 1.13)	-1.6 (-11.8, 8.7)

Source: Table 35, p83 of the submission.
CP = chemotherapy (carboplatin + paclitaxel); RR = relative risk; RD = risk difference; TEAE = treatment-emergent adverse event
Note: Bold values indicate results where the 95% CI did not include the null.

6.25 A summary of other key AEs is presented in Table 7. The most common immune-related AEs reported in POD1UM-303 were hypothyroidism (14.3% for retifanlimab + CP vs 3.3% for placebo + CP), other nervous system AEs (12.3% for retifanlimab + CP vs 10.5% for placebo + CP), skin reactions (11.7% for retifanlimab + CP vs 9.2% for placebo + CP) and colitis (10.4% for retifanlimab + CP vs 3.9% for placebo + CP).

Table 7: POD1UM-303, other key adverse events during the randomised treatment period (safety population)

Patients (n [%]) with:	Retifanlimab + CP (N = 154)	Placebo + CP (N = 152)	RR (95% CI)	RD (95% CI)
Most frequent Grade 3 or higher TEAEs occurring in > 5% of patients in the retifanlimab + CP arm				
Patients with a grade 3 or higher TEAE	128 (83.1)	114 (75.0)	1.11 (0.99, 1.24)	8.1 (-1.0, 17.2)
Neutropenia	54 (35.1)	45 (29.6)	1.18 (0.85, 1.64)	5.5 (-5.0, 15.9)
Anaemia	30 (19.5)	31 (20.4)	0.96 (0.61, 1.50)	-0.9 (-9.9, 8.0)
Neutrophil count decreased	26 (16.9)	13 (8.6)	**1.97 (1.05, 3.70)**	**8.3 (0.9, 15.7)**
White blood cell count decreased	14 (9.1)	13 (8.6)	1.06 (0.52, 2.19)	0.5 (-5.8, 6.9)
Diarrhoea	8 (5.2)	9 (5.9)	0.88 (0.35, 2.21)	-0.7 (-5.9, 4.4)
Sponsor-assessed irAEs				
irAE	75 (48.7)	40 (26.3)	**2.66 (1.65, 4.29)**	**1.85 (1.36, 2.53)**
Retifanlimab/placebo-related irAE	54 (35.1)	23 (15.1)	**3.03 (1.74, 5.27)**	**2.32 (1.50, 3.57)**
Serious irAE	18 (11.7)	7 (4.6)	**2.74 (1.11, 6.77)**	**2.54 (1.09, 5.90)**
Grade 3 or higher irAE	21 (13.6)	9 (5.9)	**2.51 (1.11, 5.67)**	**2.30 (1.09, 4.87)**
Fatal irAE	0 (0.0)	0 (0.0)	-	-
Serious retifanlimab/placebo-related irAE	15 (9.7)	4 (2.6)	**3.99 (1.29, 12.32)**	**3.70 (1.26, 10.90)**
Grade 3 or higher retifanlimab/placebo-related irAE	17 (11.0)	6 (3.9)	**3.02 (1.16, 7.88)**	**2.80 (1.13, 6.90)**
Retifanlimab/placebo dose delayed due to irAE	9 (5.8)	2 (1.3)	4.66 (0.99, 21.91)	4.44 (0.98, 20.22)
irAE leading to discontinuation of retifanlimab/placebo	10 (6.5)	0 (0.0)	-	-
Chemotherapy-related irAE	30 (19.5)	25 (16.4)	1.23 (0.68, 2.21)	1.18 (0.73, 1.92)
irAE leading to discontinuation of chemotherapy	5 (3.2)	1 (0.7)	5.07 (0.58, 43.89)	4.94 (0.58, 41.75)
irAEs occurring in >10% of patients in the retifanlimab + CP arm				
Hypothyroidism	22 (14.3)	5 (3.3)	**4.34 (1.69, 11.17)**	**11.0 (4.8, 17.2)**
Other, nervous system	19 (12.3)	16 (10.5)	1.17 (0.63, 2.19)	1.8 (-5.3, 8.9)
Skin reactions	18 (11.7)	14 (9.2)	1.27 (0.65, 2.46)	2.5 (-4.4, 9.3)
Colitis	16 (10.4)	6 (3.9)	**2.63 (1.06, 6.55)**	**6.4 (0.7, 12.2)**

Source: Tables 35, 36, 39 and 41 pp83, 84, 88 and 97 of the submission.
CI = confidence interval; CP = chemotherapy (carboplatin + paclitaxel); irAE, immune-related adverse event; N = total participants in group; RR = relative risk; RD = risk difference; TEAE = treatment-emergent adverse event
Note: **Bold** values indicate results where the 95% CI did not include the null.

6.26 Overall, the submission considered that safety results from POD1UM-303 supports the claim that retifanlimab + CP was inferior in safety to placebo + CP (or CP alone).

Benefits/harms

6.27 A summary of the comparative benefits and harms for retifanlimab + CP versus placebo + CP is presented in Table 8.

Table 8: Summary of comparative benefits and harms for retifanlimab + CP and placebo + CP

Benefits					
Progression-free survival (median duration of follow up 7.57/7.13 months[a]					
Event		**retifanlimab + CP**	**placebo + CP**	**HR (95% CI)**	
Progressed, n (%)		92/154 (59.7)	110/154 (71.4)	0.63 (0.47, 0.84), p=0.0006 [b]	
Median PFS, months (95% CI)		9.3 (7.5, 11.3)	7.4 (7.1, 7.7)		
% not progressed at 12 months (95% CI)		41.2 (32.7, 49.6)	21.9 (14.9, 29.7)		
Harms					
retifanlimab + CP	**placebo + CP**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
			retifanlimab + CP	**placebo + CP**	
Any retifanlimab/placebo-related TEAE					
138/154	118/154	1.15 (1.04, 1.28)	89.6	77.6	12.0 (0.01, 0.24)
Serious retifanlimab/placebo-related TEAE					
25/154	10/152	2.47 (1.23, 4.96)	16.2	6.6	9.7 (2.6, 16.7)
Immune-related adverse event					
75/154	40/152	2.66 (1.65, 4.29)	48.7	26.3	1.85 (1.36, 2.53)
Serious immune-related adverse event					
18/154	7/152	2.74 (1.11, 6.77)	11.7	4.6	2.54 (1.09, 5.90)
Hypothyroidism					
22/154	5/152	4.34 (1.69, 11.17)	14.3	3.3	11.0 (4.8, 17.2)

Source: Tables 30, 31, pp72, 74 of the submission.
CP = chemotherapy (carboplatin-paclitaxel); HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio; OS = overall survival; PFS = progression-free survival; TEAE = treatment-emergent adverse event
[a] Median duration of follow-up: retifanlimab + CP = 7.57 months; placebo + CP = 7.13 months
[b] HR from stratified Cox model. P-value from stratified log-rank test. PFS was tested at the 1-sided 2.5% level.

6.28 On the basis of the direct comparative evidence presented by the submission for POD1UM-303, for every 100 patients treated with retifanlimab + CP in comparison with placebo + CP:

- Approximately 19 additional patients will have remained progression free after 12 months;
- Approximately 12 additional patients will have a treatment related TEAE;
- Approximately 10 additional patients will have a serious treatment related TEAE;
- Approximately 2 additional patients will have an immune-related AE;
- Approximately 3 additional patients will have a serious immune-related AE; and
- Approximately 11 additional patients will have hypothyroidism.

Clinical claim

6.29 The submission described retifanlimab + CP as superior in terms of effectiveness compared to CP and inferior in terms of safety compared to CP. The evaluation and the ESC considered that the overall claim of superior effectiveness was supported by the direct evidence presented in POD1UM-303. In particular, the evaluation and the ESC considered the claim was:

- supported by the PFS results of POD1UM-303. Patients randomised to retifanlimab + CP reported a statistically significant PFS benefit compared to

patients randomised to placebo + CP (HR = 0.63 [95% CI: 0.47, 0.84]; p = 0.0006), thereby meeting the trial's primary endpoint.

- inadequately supported by the OS results for POD1UM-303 as the OS HR of 0.70 (95% CI: 0.49, 1.01); p = 0.0273 was not statistically significant, and the limitations with the *post hoc* IPCW and RPSFT OS crossover adjustments meant the OS adjusted results were highly uncertain (see paragraph 6.17 - 6.18).

Therefore, the evaluation and the ESC considered that the magnitude of OS benefit was highly uncertain.

6.30 The evaluation and the ESC considered that the submission's claim that retifanlimab + CP is inferior in terms of safety compared to placebo + CP was reasonable. AEs were more commonly observed to occur in the retifanlimab + CP arm of POD1UM-303. For example, in the retifanlimab + CP arm there was a higher rate of retifanlimab/placebo-related TEAEs (RR 1.15; 95% CI 1.04, 1.28), serious retifanlimab/placebo-related TEAEs (RR 2.47; 95% CI 1.23, 4.96) and treatment discontinuation due to TEAE (RR 4.19; 95% CI 1.44, 12.18) compared to the placebo + CP arm. There were also more immune related AEs in patients treated with retifanlimab + CP compared to placebo + CP, which the ESC noted is consistent with other single agent immunotherapy agents.

6.31 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

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

Economic analysis

6.33 The submission presented a stepped economic evaluation based on one direct randomised trial (POD1UM-303). The type of economic evaluation presented was a cost-utility analysis that compared retifanlimab + CP versus placebo + CP. Details of the key components of the economic evaluation are summarised in Table 9.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Retifanlimab + CP vs placebo + CP
Time horizon	15 years in the model base case versus 14.77 months in trial[a]
Type of analysis	Cost-utility analysis
Outcomes	PFS, OS, *QALYs, LYG*
Methods used to generate results	Partitioned survival model
Health states	Progression-free; Progressed disease; Dead
Cycle length	28 days
Allocation to health states	Health state allocation over time is determined by PFS and OS curves from the POD1UM-303 trial (using RPSFT crossover adjustment for OS), extrapolated over the modelled time horizon via joint fitted parametric survival models (PFS: Lognormal; OS: Loglogistic).
Extrapolation method	Parametric survival functions were fitted to the OS and PFS KM data from the POD1UM-303 trial-based on individual patient data. A parametric model was fitted to each treatment arm with Lognormal selected in base case for PFS (both arms) and Loglogistic selected for OS for both arms) based on goodness of fit and the assumption of proportional hazards. In the base case, risk convergence and curve convergence were not included. 76.4% of the incremental LYGs occur in the extrapolated period.
Health related quality of life	Utility values were applied to each of the key health states based on POD1UM-303. pre-progression = 0.872; post-progression = 0.769

Source: Tables 53, 65, pp114, 140 of the submission.
LYG = life years gained; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life years; RPSFT = rank-preserving structural failure time
[a] In POD1UM-303, the OS median follow-up duration for the retifanlimab + CP arm was 14.77 months and the OS median follow-up duration for the placebo + CP arm was 12.86 months.

6.34 The model base case assumed a 15-year time horizon, which the submission justified as a lifetime horizon based on extrapolated POD1UM-303 OS data. The submission also claimed that this was supported by the estimation that 2.5% of patients on current standard of care (i.e. the CP arm) were estimated to remain alive beyond 15 years. The evaluation and the ESC considered that a 15-year lifetime time horizon may be overly optimistic, given the limited OS follow-up in POD1UM-303 (14.77 months for the retifanlimab + CP arm and 12.86 months for the placebo + CP arm), and extrapolation to 15 years would substantially increase uncertainty, especially as the POD1UM-303 unadjusted OS analysis was not statistically significant at the DCO. Assuming a 7.5 or 10-year time horizon increased the ICER by [redacted]% and [redacted]%, respectively. The Pre-PBAC response indicated the sponsor was willing to accept a 10-year time horizon in a re-specified base case (see paragraph 6.48).

6.35 Moreover, no convergence was assumed in the base case to account for the uncertainty in extrapolation, though these were included as sensitivity analyses. The PSCR argued that the curves have essentially converged at 15 years, as only 2.4% of patients in the CP arm and 4.7% in the retifanlimab + CP arm were estimated to be alive. However, the ESC noted that at this time the OS rate observed for the retifanlimab + CP arm was approximately double that for the placebo + CP arm. The ESC considered the assumed continued survival benefit associated with retifanlimab (which has a treatment duration of up to 12 months) was optimistic, given the relatively immature OS data (with a median trial follow-up of less than 15 months for OS). Thus, the ESC considered that risk convergence from 5 years would be more reasonable. The ESC noted the ICER was not sensitive to the inclusion of curve convergence (even when corrected during evaluation) as this method applies a linear rate of decline in OS and PFS for retifanlimab + CP, whereas the POD1UM-303 Kaplan-Meier survival data did not follow a linear pattern.

6.36 Parametric survival functions were fitted to the OS and PFS KM data from the POD1UM-303 trial-based on individual patient data. The base case relied on OS data adjusted for crossover using the RPSFT analysis, while the analysis using the ITT population and adjusting for cross-over using IPCW were presented as a sensitivity analyses. The ESC considered it was not reasonable to use the crossover-adjusted OS data in the base case, as these were post hoc analyses with substantial uncertainties and it was likely that the required assumptions were not met. In particular for RPSFT, the constant treatment effect assumption was likely violated as 2L (retifanlimab monotherapy) may be less effective compared to 1L (retifanlimab + carboplatin + paclitaxel (CP)) (see paragraphs 6.17 to 6.18). In the absence of more reliable data, the evaluation and the ESC considered it may be reasonable to use the POD1UM-303 ITT OS results (which had a more conservative point estimate for OS HR) as a proxy, despite the lack of statistical significance, as the base case. The model was moderately sensitive to the use of RPSFT OS results instead of the ITT results, as using the ITT OS results (using the loglogistic function for extrapolation for both RPSFT and ITT) increased the ICER by [redacted]%.The PSCR argued that the very existence of any survival gain in favour of retifanlimab means that crossover will confound the OS HR point estimate and render the ITT OS HR incorrect. However, the ESC considered that, while the crossover adjusted results were informative sensitivity analyses, it would be more reasonable to use the POD1UM-303 ITT OS results in the base case. The Pre-PBAC response indicated the sponsor was willing to accept use of the ITT analysis in a re-specified base case (see paragraph 6.486.49).

6.37 The submission concluded that the proportional hazards assumption does not appear to be violated based on the Schoenfeld residuals and log-log plots, and therefore joint parametric functions were applied in the base case for PFS and OS.

6.38 For PFS and OS, the submission applied the Lognormal and Loglogistic models in the base case, respectively, based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC). The model was moderately sensitive to the choice of extrapolation function for OS. The evaluation considered that visually, all extrapolations had reasonable fit to the Kaplan-Meier data from POD1UM-303. The submission claimed that the Gompertz and Weibull models for OS likely underestimate long-term survival (as both models estimated less than 6% survival at 5 years in the CP arm whereas NCCN anal cancer guidelines [version 4.2025] report a 30% survival at 5 years).

6.39 The time point at which the model switches from POD1UM-303 KM data to parametric extrapolation was determined by the Gebski criterion (Gebski 2018[6]) with consideration also given to visual observation of the KM data and median trial follow-up. The submission used Gebski criterion 1 (2.5%) in the base case, and Gebski criterion 1 (5%) and Criterion 2 in sensitivity analyses. The KM timepoints corresponding to these Gebski criteria as presented in the submission are shown in Table 10.

Table 10: Kaplan-Meier time points (months) prior to failing Gebski criterion

	KM time point (months) prior to failing Criterion			POD1UM-303 Median follow-up (months)[b]
	Criterion 1 (2.5%)	Criterion 1 (5%)	Criterion 2	
Progression-free survival				
Retifanlimab + CP arm	24.1	29.8	31.3	7.57
CP arm	23.1	26.0	26.0	7.13
Overall survival				
Retifanlimab + CP arm	27.3	31.5	34.0	14.77
CP arm	28.3[a]	32.4	32.7	12.86

Source: Table 30, p72, Table 31, p75 and Table 63, p138 of the submission.
CP = carboplatin-paclitaxel; KM = Kaplan-Meier
[a] In the model base case, OS for the CP arm was adjusted for crossover and was equal to 25.2.
[b] The median follow-up from POD1UM-303 was presented for comparison.

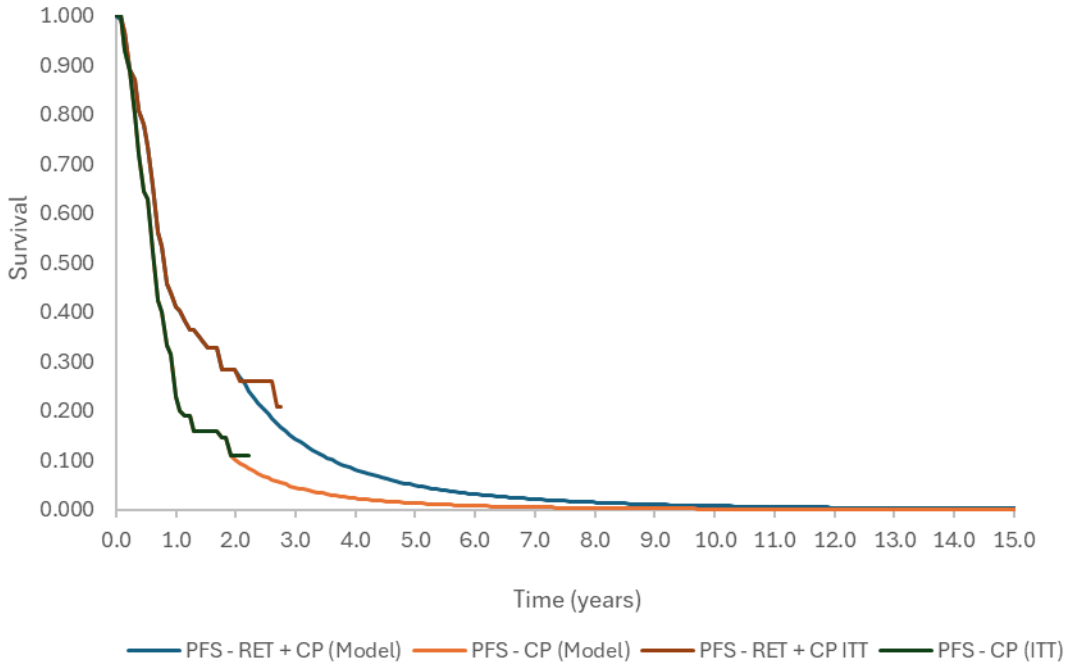
6.40 Use of the Gebski criterion 1 (2.5%) in the model base case was the least conservative of the 3 methods investigated in the submission with regards to the incremental cost effectiveness ratio (ICER), and resulted in a shorter duration of use of the POD1UM-303 KM data compared to Gebski criterion 1 (5.0%) and Gebski criterion 2, which increased the ICER by [redacted]%, and [redacted]%, respectively.

[6] Gebski V et al. Data maturity and follow-up in time-to-event analyses. International Journal of Epidemiology. 2018; 47(3), pp850-859, https://doi.org/10.1093/ije/dyy013

6.41 The submission claimed that visual inspection of the OS KM curves indicated it would be biased against retifanlimab + CP to include KM data post 29 months due to a 6.8% drop in survival occurring as a result of a single death among 14 patients. The PSCR reiterated the view that Gebski criterion 1 (2.5%) was the most appropriate, citing consistent incremental differences in survival at earlier time points (e.g., 13.1% at 12 months, 11.2% at 18 months, and 12.4% at 24 months, based on ITT). The PSCR stated 'the inclusion of this drop in retifanlimab + CP survival is considered to bias results in favour of CP, and should not be included when based on the small number of patients remaining at risk at that point of the trial.' However, the ESC noted that at 29 months, neither the Criterion 1 (5%) nor Criterion 2 thresholds had been breached, suggesting continued used of observed KM data past 29 months may be reasonable.

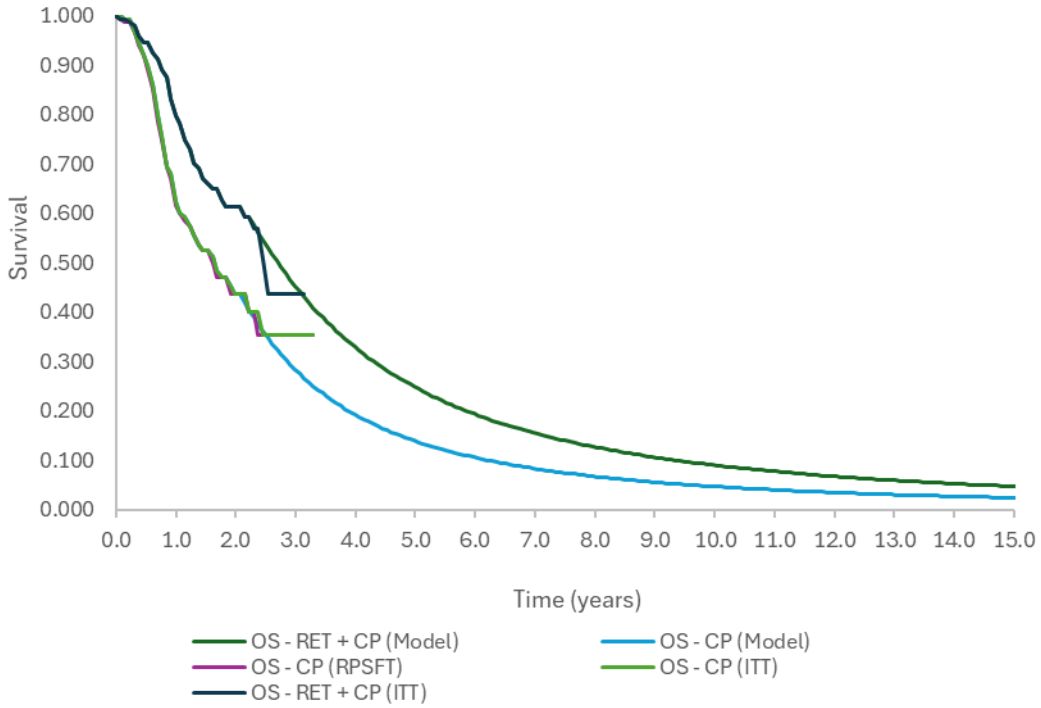
6.42 The PFS and OS survival curves used in the model base case and the POD1UM-303 ITT data (as well as the OS for the CP arm using RPSFT) are illustrated in Figure 3 and Figure 4, respectively.

Figure 3: PFS curves for the model base case and POD1UM-303 ITT data



Source: Figure 37, p139 of the submission, modified during the evaluation using Retifanlimab_SCAC_CUA.xlsx.
CP = carboplatin-paclitaxel; ITT = intention to treat; PFS = progression-free survival; RET = retifanlimab.

Figure 4: OS curves for the model base case and POD1UM-303 ITT and RPSFT data



Source: Figure 37, p139 of the submission, modified during the evaluation using Retifanlimab_SCAC_CUA.xlsx.
CP = carboplatin-paclitaxel; ITT = intention to treat; OS = overall survival; RET = retifanlimab.

6.43 The submission applied utility values of 0.872 (PF) and 0.769 (PD) in the model base case based on POD1UM-303 EQ-5D-5L data observations. The evaluation noted the number of data points for post-progression utilities was substantially lower than for pre-progression, thereby increasing uncertainty. The submission acknowledged that these values were higher than those used in previous PBAC evaluations for other squamous cell carcinomas (SCC) that obtained a positive recommendation, e.g. head and neck SCC (pembrolizumab, March 2022 PBAC meeting and nivolumab, July 2021 PBAC meeting). The evaluation considered that the difference in mapping approaches affect consistency across PBAC considerations. Given the lack of published values for utility in SCAC, the evaluation could not externally verify POD1UM-303 values. Using utilities from other SCC previously considered by the PBAC generally increased the ICER (e.g. using utilities from pembrolizumab for head and neck SCC considered at the March 2022 PBAC meeting (PF = 0.787; PD = 0.707) increased the ICER by [redacted]%).

6.44 Key drivers of the model are summarised in Table 11.

Table 11: Key drivers of the model

Description	Method/Value in submission base case	Impact Base case: $[redacted][1]/QALY gained
Duration of KM data	The model base case used Gebski criterion 1 (2.5%) to determine the duration for which the POD1UM-303 KM data was used.	High, favours retifanlimab. Use of Gebski criterion 1 (5%) increased the ICER to $[redacted][2] (+[redacted]%). Use of Gebski criterion 2 increased the ICER to $[redacted][3] (+[redacted]%).
Time horizon	The model used a time horizon of 15 years, whereas the OS follow-up in POD1UM-303 OS was 14.77 months for the retifanlimab + CP arm and 12.86 months for the placebo + CP arm.	Moderate, favours retifanlimab. Use of a 7.5-year time horizon increased the ICER by [redacted]% to $[redacted][3].
OS parametric model	The model used the loglogistic model in the base case to extend the POD1UM-303 OS KM data.	Moderate, uncertain which drug is favoured. Use of the Gompertz parametric model increased the ICER to $[redacted][2] (+[redacted]%). Use of the exponential parametric model decreased the ICER to $[redacted][4] (-[redacted]%)
Doses of retifanlimab	The model base case assumed that patients received 9 infusions of retifanlimab (median number of doses in POD1UM-303).[a]	Moderate. Inclusion of 13 retifanlimab infusions (maximum dose) increased the ICER to $[redacted][5] (+[redacted]%). Using PFS to inform duration of treatment (as used for the retifanlimab for MCC submission which was also considered at the November 2025 PBAC meeting) increased the ICER by [redacted]%
Approach to OS crossover adjustment	The base case model used the RPSFT model to adjust for crossover instead of the ITT results.	Moderate, favours retifanlimab. Use of the ITT OS data increased the ICER to $[redacted][3] (+[redacted]%).
Risk convergence	The base case model did not include risk convergence between the survival curves for the treatment arms.	Moderate, favours retifanlimab. Inclusion of risk convergence from 3 years increased the ICER to $[redacted][3] (+[redacted]%).

Source: Constructed during evaluation using Table 90, p159 of the submission and Retifanlimab_SCAC_CUA.xlsx
CP = carboplatin-paclitaxel; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; KM = Kaplan-Meier; MCC = Merkel Cell Carcinoma; OS = overall survival; RET = retifanlimab. RPSFT = rank preserving structural failure time
[a] The mean number of doses was 8.5, so the use of the median number of doses was conservative, refer to Table 13).
The redacted values correspond to the following ranges:
[1] *$75,000 to < $95,000*
[2] *$115,000 to < $135,000*
[3] *$95,000 to < $115,000*
[4] *$55,000 to < $75,000*
[5] *$135,000 to < $155,000*

6.45 The model base case (in the submission) estimated an ICER of $75,000 to < $95,000 per QALY for retifanlimab + CP compared to placebo + CP in inoperable locally advanced recurrent or metastatic SCAC. A summary of the results of the stepped economic evaluation is presented in Table 12.

Table 12: Stepped economic evaluation – submission model

Step	Costs	Outcomes	Incremental costs	Incremental outcomes	ICER
Step 1: Trial-based analysis over 24 months	Drug and administration costs	PFLY	$[redacted]	0.270	$[redacted][1]
		LY		0.223	$[redacted][1]
Step 2: Translation of survival outcomes to QALYs	Drug and administration costs	QALY	$[redacted]	0.199	$[redacted][2]
		LY		0.223	$[redacted][1]
Step 3: Extrapolation over the 15-year time horizon	Drug and administration costs	QALY	$[redacted]	0.784	$[redacted][3]
		LY		0.946	$[redacted][4]
Step 4: Inclusion of other healthcare resource use	Direct healthcare costs	QALY	$[redacted]	0.784	$[redacted][4]
		LY		0.946	$[redacted][4]

Source: Table 85, p154 of the submission.
ICER = incremental cost-effectiveness ratio; LY = life year; PFLY = progression-free life year; QALYs = quality adjusted life years
The redacted values correspond to the following ranges:
[1] *$255,000 to < $355,000*
[2] *$355,000 to < $455,000*
[3] *$95,000 to < $115,000*
[4] *$75,000 to < $95,000*

6.46 The extrapolation of the time horizon from 24 months to 15 years (step 2 to step 3) had a considerable impact on the number of life years (LYs) and quality-adjusted life years (QALYs) accrued but had little impact on costs, as drug, administration and safety costs were incurred at the start of the model. The incremental LYs gained increased from 0.223 to 0.946 and therefore 76.4% of the incremental LYs were accrued during the extrapolated period.

6.47 The results of key univariate and multivariate sensitivity analyses are summarised in Table 13 and Table 14, respectively.

Table 13: Key univariate sensitivity analyses (based on submission model)

Analyses	Incremental costs	Incremental QALYs	ICER	% change from base case
Base case	**$[redacted]**	**0.784**	**$[redacted][1]**	**-**
Time horizon (base case: 15 years)				
7.5 years	$[redacted]	0.644	$[redacted][2]	[redacted]%
10 years	$[redacted]	0.715	$[redacted][2]	[redacted]%
Discount rate (base case: 5% per annum)				
0%	$[redacted]	0.967	$[redacted][1]	-[redacted]%
3.5%	$[redacted]	0.832	$[redacted][1]	-[redacted]%
Approach to OS crossover adjustment (base case: RPSFT)				
ITT OS (no crossover costs) [a]	$[redacted]	0.667	$[redacted][2]	[redacted]%
IPCW	$[redacted]	0.866	$[redacted][1]	-[redacted]%
Duration of KM data (base case: Gebski criterion 1 (2.5%))				
Gebski Criterion 1 (5%)	$[redacted]	0.560	$[redacted][3]	[redacted]%
Gebski Criterion 2	$[redacted]	0.674	$[redacted][2]	[redacted]%
OS parametric model (base case: Loglogistic)				
Exponential	$[redacted]	0.990	$[redacted][4]	-[redacted]%
Weibull [b]	$[redacted]	0.707	$[redacted][2]	[redacted]%
Gompertz[b]	$[redacted]	0.619	$[redacted][3]	[redacted]%
Extrapolation assumptions (base case: no convergence)				
PFS and OS risk convergence from 3 years	$[redacted]	0.673	$[redacted][2]	[redacted]%
PFS and OS risk convergence from 5 years	$[redacted]	0.754	$[redacted][2]	[redacted]%
Utility values (base case: PF = 0.872; PD = 0.769)				
March 2022 HNSCC pembrolizumab PSD (PF = 0.787; PD = 0.707)	$[redacted]	0.713	$[redacted][2]	[redacted]%
July 2021 OSCC nivolumab PSD (immunotherapy PF = 0.796; chemotherapy PF = 0.737; PD = 0.551)	$[redacted]	0.710	$[redacted][2]	[redacted]%
Doses per course of treatment (base case: median doses from POD1UM-303 = 9 doses of retifanlimab, 6 doses of carboplatin and 15 doses of paclitaxel for both treatment arms)				
Mean doses POD1UM-303 [c]	$[redacted]	0.784	$[redacted][1]	-[redacted]%
Using PFS to inform ToT with retifanlimab [d]	$[redacted]	0.784	$[redacted][2]	[redacted]%
13 infusions of retifanlimab (maximum allowed under proposed restriction)	$[redacted]	0.784	$[redacted][5]	[redacted]%

Source: Tables 89, 90, 91, 92, pp157-160 of the submission and Retifanlimab_SCAC_CUA.xlsx.

CP = chemotherapy; HNSCC = head and neck squamous cell carcinoma; ICER = incremental cost-effectiveness ratio; IPCW = inverse probability of censoring weighting; ITT = intention-to-treat; OS = overall survival; OSCC = oesophageal squamous cell carcinoma; PD = progressive disease; PF = progression-free; PFS = progression-free survival; PSD = public summary document; QALY = quality adjusted life year; RPSFT = rank preserving structural failure time; SCAC = squamous cell anal carcinoma; ToT = Time on Treatment

[a] No second-line retifanlimab drug costs included in scenario.

[b] Submission claimed that Gompertz and Weibull models are likely to underestimate long-term survival, as both models estimate less than 6% survival at 5 years in the CP arm (<1% by 8 years) compared to 5-year survival of 10-20% reported for metastatic SCAC in clinical practice (Cancer Research UK 2025; Dewdney 2012).

[c] Retifanlimab: 8.5 doses; Carboplatin: RET+CP arm 5.2 doses, CP arm 5.0 doses; Paclitaxel: RET+CP and CP arms 13.4 doses.

[d] Total cost for retifanlimab for 13 cycles calculated to be $[redacted].

The redacted values correspond to the following ranges:

[1] *$75,000 to < $95,000*

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

[3] *$115,000 to < $135,000*

[4] *$55,000 to < $75,000*

[5] *$135,000 to < $155,000*

Table 14: Multivariate sensitivity analyses using different Gebski criteria (with no crossover adjustment for OS, risk convergence from 5 years and a 10 year time horizon)

Analyses	Incremental costs	Incremental QALYs	ICER	% change from base case
Base case (Gebski Criterion 1 [2.5%], no convergence, 15-year time horizon, RPSFT for OS, price $[redacted]/vial)	**$[redacted]**	**0.784**	**$[redacted][1]**	**-**
• 10-year time horizon • no crossover adjustment for OS (ITT)	$[redacted]	0.605	$[redacted][2]	[redacted]%
• Gebski criterion 2 • no crossover adjustment for OS (ITT) • risk convergence[a] from 5 yrs • 10-yr time horizon	$[redacted]	0.407	$[redacted][3]	[redacted]%
• no crossover adjustment for OS (ITT) • risk convergence[a] from 5 yrs • 10 yr time horizon	$[redacted]	0.590	$[redacted][2]	[redacted]%
• Gebski Criterion 1 (5%) • no crossover adjustment for OS (ITT) • risk convergence [a] from 5 yrs • 10 yr time horizon	$[redacted]	0.359	$[redacted][3]	[redacted]%
Pre-PBAC Revised base case (Gebski Criterion 1 [2.5%], no convergence, **10-year time horizon, no crossover adjustment for OS (ITT), price $[redacted]/vial**)	$[redacted]	0.605	$[redacted][1]	0
• Gebski criterion 2 • risk convergence[a] from 5 yrs	$[redacted]	0.407	$[redacted][4]	[redacted]%
• risk convergence[a] from 5 yrs	$[redacted]	0.590	$[redacted][5]	[redacted]%
• Gebski Criterion 1 (5%) • risk convergence [a] from 5 yrs	$[redacted]	0.359	$[redacted][3]	[redacted]%

Source: Constructed during evaluation using Retifanlimab_SCAC_CUA.xlsx.
ITT = intention to treat; OS = overall survival; RPSFT = rank preserving structural failure time; yr = year.
[a] Risk convergence as applied by the submission's sensitivity analyses assumes that, after a particular time point, the PFS and/or OS HR between retifanlimab and avelumab immediately becomes 1 (i.e. the rate of change in PFS and OS for avelumab is applied to both avelumab and retifanlimab) until the end of the time horizon.
The redacted values correspond to the following ranges:
[1] *$75,000 to < $95,000*
[2] *$115,000 to < $135,000*
[3] *$155,000 to < $255,000*
[4] *$135,000 to < $155,000*
[5] *$95,000 to < $115,000*

6.48 The evaluation and the ESC considered that overall, the results from the economic model presented in the submission were uncertain, and may have favoured retifanlimab for the following reasons:

- A 15-year time horizon may be overly optimistic and uncertain, as outlined in paragraph 6.34. The ESC considered a 10-year time horizon to be more appropriate to help account for uncertainty in long term outcomes. The Pre-PBAC response indicated that '(t)he Sponsor is willing to adopt a truncated 10-year time horizon in a revised base case to help account for uncertainty in long term outcomes'.

- The base case model applied POD1UM-303 OS data based on the RPSFT post hoc analysis, however the assumption of a constant treatment effect was likely violated (i.e. considering that 2L (retifanlimab) may be less effective compared to 1L retifanlimab + CP, as outlined in paragraph 6.36). In the absence of more reliable data, the evaluation and the ESC considered it may be reasonable to use the POD1UM-303 ITT OS results as the base case. The Pre-PBAC response maintained the view that the ITT analysis underestimates OS benefit due to crossover, but indicated that the Sponsor 'is willing to adopt the ITT analysis in a revised base case'.
- The model's base case did not include risk convergence. Even with the shorter time horizon of ten years, the ESC considered the assumed continued survival benefit associated with retifanlimab was optimistic, given the relatively immature OS data (with a median trial follow-up of less than 15 months for OS). Thus, the ESC considered that risk convergence from 5 years would be more reasonable. The Pre-PBAC response argued that it considered it would be overly conservative to apply the 'arbitrary assumption of risk convergence in the model' in addition to the 10-year time horizon and use of ITT analysis in the revised base case.
- While the submission claimed it was inappropriate to use the retifanlimab + CP OS KM data for more than 29 months in the model, Gebski criterion 1 (5%) and Gebski criterion 2 had not been met at this time point (with the retifanlimab + CP arm KM data used until 31.5 months and 34.0 months for these criteria, respectively), as outlined in paragraphs 6.40 - 6.41. The ESC considered it may be reasonable to continue to use observed KM data past 29 months (i.e. Gebski 1 (5%) cutoff or Gebski 2). The Pre-PBAC response maintained that the use of Gebski 1 (5%) or Gebski 2 bias against retifanlimab due to the inclusion of a 6.8% drop in survival at 29 months, which reduces the ITT incremental OS from 11.4% to 4.6% when <10% remain at risk.

6.49 The Pre-PBAC response presented a revised base case with a 10-year time horizon and ITT analysis of OS data, and a [redacted]% price reduction to $[redacted] per 500 mg vial (from $[redacted]), resulting in an ICER of $75,000 to < $95,000 per QALY for the revised base case.

Drug cost/patient/course

6.50 Drug costs per patient for retifanlimab are summarised in Table 15. These are based on the drug costs proposed in the submission.

Table 15: Drug cost per patient for retifanlimab + CP and placebo + CP (based on price proposed in submission)

	RET + CP Trial dose and duration	RET + CP Model	RET + CP Financial estimates	Placebo + CP Trial dose and duration	CP Model	CP Financial estimates
Total dose RET	8.5 infusions 499.8 mg mean (med. 9.0 infusions, 500.0 mg)	9 infusions	9 infusions	NA	NA	NA
Mean duration RET	7.476 mo. (median 7.409 mo.)	NA	8.279 mo.	NA	NA	NA
Mean dose carboplatin	5.2 infusions 508.0 mg (med. 6.0 infusions, 493.0 mg)	6 infusions 559 mg [a]	Not included [b]	5.0 infusions 515.6 mg (med. 6.0 infusions, 500.0 mg)	6 infusions 559 mg [a]	Not included [b]
Mean duration carboplatin	4.186 months (med. 4.632 mo.)	NA	Not included	3.997 mo. (med. 4.632 mo.)	NA	Not included
Mean dose paclitaxel	13.4 infusions 132.6 mg (med. 15.0 infusions, 132.0 mg)	15 infusions 139.2 mg [c]	Not included [b]	13.4 infusions 131.5 mg (med. 15.0 infusions, 130.3 mg)	15 infusions 139.2 mg [c]	Not included [b]
Mean duration paclitaxel	4.481 mo. (med. 5.2092 mo.)	NA	Not included	4.380 mo. (med. 5.092 mo.)	NA	Not included
Total cost/ patient/ course [h]	$[redacted] [d]	$[redacted] [e]	$[redacted]	$3,413 [e, f]	$3,413 [e, f]	$0

Source: Constructed during the evaluation using Tables 21, 23 and 24, pp55, 58 and 59 of the submission, Retifanlimab_SCAC_CUA.xlsx and Retifanlimab_SCAC_BIM.xlsx

BSA = body surface area; CP = carboplatin + paclitaxel; GFR = glomerular filtration rate; med. = median mo. = month; NA = not applicable; RET = retifanlimab

[a] Calculated using the Calvert formula, based on dose of 5 AUC and average GFR of 86.8, based on mean creatinine clearance at baseline for all patients in POD1UM-303.

[b] Carboplatin and paclitaxel costs were not included in the financial estimates. The submission assumed these costs would be unchanged even if retifanlimab is PBS listed.

[c] Calculated based on 80mg/m^2 dose and mean BSA of 1.74 m^2.

[d] Based on mean trial doses.

[f] Cost of carboplatin calculated including wastage (based on two 450 mg vials of carboplatin per dose). Cost of paclitaxel calculated including wastage (one 300 mg vial).

[g] Cost of carboplatin and paclitaxel are the same for trial dose and model because wastage is included.

[h] retifanlimab costs based on submission vial price of $[redacted]/vial

Estimated PBS usage & financial implications

6.51 This submission was considered by DUSC.

6.52 The submission used an epidemiological approach for estimating the size of the eligible patient population. As discussed in paragraph 4.3, the submission considered that there were four populations who would be eligible for retifanlimab under the proposed listing and estimated the incident patient population for each of these four populations.

6.53 The key inputs used for the financial estimates are summarised in Table 16.

Table 16: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Incident patients QAN with anal cancer	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]	2024 AIHW anal cancer incidence (actual cases 2010-2020 and projected cases 2021-2024). The submission estimated anal cancer cases for 2025-2031 based on linear extrapolation of the AIHW data. [b]	DUSC considered the submission's estimates were underestimated due to: • linear extrapolation of the AIHW data to determine the number of cases of anal cancer after 2024, rather than using the published AIHW projections [c], which predicted 683 incident patients in 2026 and 862 in 2034. DUSC considered that the submission underestimated incident cases compared to AIHW by ~8% by yr 6. • more conservative growth assumptions, i.e. 2.4%/yr (submission) vs 3.2%/yr (AIHW).
Of patients with anal cancer, the % with SCAC at diagnosis	71.8%	Soeberg 2015 [d]	The evaluation considered this was likely underestimated, as other sources have reported that 75% to 95% of anal cancer is SCAC (Pedersen 2025). DUSC considered the proportion likely to be ~85-90%, based on a brief literature review, noting that Soeberg 2015 is only based on NSW data with linear projections from 2009 to 2014. PBAC considered this should be amended to 85%, consistent with the pre-PBAC response.
Incidence of metastatic SCAC at diagnosis (population 1) [a]	8.9%	Soeberg 2015 [d]	DUSC and PBAC considered this was reasonable.
Incidence of locoregional SCAC (populations 2 and 3)	91.1%	Soeberg 2015	
Progression rates			
Progression rate locoregional to metastatic disease (population 2)	Annual range: 0.1% - 7.0%	Based on digitised survival data and relapse data for patients receiving chemotherapy from Northover 2010. [e]	While the Year 2 progression rates were considerably higher than for any other year, Rao 2021 (ESMO anal cancer guidelines) states that the majority of tumours that recur typically do so within 24 months following completion of CRT, so may be plausible. DUSC considered the progression rates were uncertain, but may be reasonable, noting:
Progression rate from locoregional to locally recurrent disease (population 3)	Annual range: 0.1% - 22.1%		

Data	Value	Source	Comment
			• the Year 2 annual progression rates were hard to validate. Confirmed in clinical guidelines that reoccurrence occurs in 24 months but no data on the number of tumours. • Population 2 - Literature review suggested >~10–20% of patients treated with curative-intent CRT for non-metastatic SCAC will develop distant metastases. Submission used the lower end of the estimates. • Population 3 – the submission indicated 32.7% over time, the literature is limited but suggested 14-35% within 24 months (Nilson et al 2020, Shakir et al 2019).
Incidence of inoperable disease in patients with locally recurrent SCAC (population 3)	21.2%	Renehan 2005 [f]	The evaluation considered this may be reasonable but could not be externally validated. Given the age of the literature source (20 years), there may be improvements in surgery techniques and the proportion of patients with inoperable disease may be uncertain. DUSC considered this input was uncertain as it could not be verified, and was likely outdated, noting: • Many studies included only operated patients. • The literature suggests a range 10-60%. However, overall the PBAC considered this input was reasonable.
Progression rate to metastatic disease after surgery for patients with locally recurrent SCAC (population 4)	Annual range: 1.5% - 9.3%	Based on digitised survival data and proportion of patients with metastatic data from Damron 2024. [g]	DUSC considered the progression rate was uncertain, noting: • The submission used 29.1% over the period. • literature overall range: ~25% to ~48% of salvaged patients later develop distant metastases. • Contemporary, larger cohort: ~48% develop distant metastases after abdominoperineal resection (APR), (Rosen et al. 2024). • Older single-centre series: ~25% develop distant metastases after APR (Schiller et al, Hallemeier et al). However, overall the PBAC considered this input was reasonable.
Treatment utilisation			
Uptake rate	[redacted]%	Assumption	The evaluation considered that a high uptake rate was likely reasonable for anal cancer treatment where chemotherapy remains standard of care. DUSC and PBAC considered this was

Data	Value	Source	Comment
			reasonable.
Retifanlimab number of doses	9 doses	Based on the median number of doses from POD1UM-303, which corresponds to 8.28 months of retifanlimab treatment.	The PBAC considered this was reasonable as it aligned with the economic model.
Chemotherapy use	Not included	The submission claimed there is not expected to be a change in the number of doses of CP dispensed for each SCAC patient if retifanlimab is listed on the PBS.	The evaluation considered that the chemotherapy costs may have been underestimated as there may be an increase in the number of patients receiving CP if retifanlimab is listed on the PBS, as a higher proportion of patients may to elect to receive 1L treatment. DUSC considered that the increase would likely be small.
Costs			
MBS costs	$126.00	MBS item number 13950	Use of MBS item 13950 was consistent with the economic model. Submission appropriately used an 80% rebate. DUSC considered this was reasonable.

Source: pp162-183 of the submission.
1L = first-line; AIHW = Australian Institute of Health and Welfare; CP = carboplatin + paclitaxel; MCC = Merkel cell carcinoma; SCAC = squamous cell anal carcinoma
[a] Incidence of locoregional SCAC at diagnosis = 100-8.9% = 91.1% (population 1).
[b] Cancer data in Australia, Data - Australian Institute of Health and Welfare AIHW data tables CDIA 2024: Book 1b.
[c] Cancer data in Australia, Data - Australian Institute of Health and Welfare AIHW data tables CDIA 2024: Book 1e.
[d] Soeberg et al. Trends in incidence and survival for anal cancer in New South Wales, Australia, 1972–2009. Cancer Epidemiology. 2015; 39(6): pp842-847. https://doi.org/10.1016/j.canep.2015.10.008
[e] Northover et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). British Journal of Cancer. 2010; 102: pp1123-1127. https://doi.org/10.1038/sj.bjc.6605605
[f] Renehan et al. Patterns of local disease failure and outcome after salvage surgery in patients with anal cancer. British Journal of Surgery. 2005; 92(5): pp605-614. https://doi.org/10.1002/bjs.4908
[g] Damron et al. Salvage Treatment of Recurrent or Persistent Anal Squamous Cell Carcinoma: The Role of Multi-modality Therapy. Clinical Colorectal Cancer. 2024; 23(1): pp85-94. https://doi.org/10.1016/j.clcc.2023.12.002
The redacted values correspond to the following ranges:
[1] 500 to < 5,000

6.54 The predicted use and financial implications associated with the proposed listing of retifanlimab is summarised in Table 17.

Table 17: Estimated use and financial implications for retifanlimab

	2026	2027	2028	2029	2030	2031
Estimated extent of use						
Patients with SCAC	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]2	[redacted]2
Patients with metastatic disease at diagnosis (population 1)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patients that progress from locoregional to metastatic disease upon first relapse (population 2)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patients that progress from locoregional to inoperable locally recurrent disease (population 3)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patients that progress from operable locally recurrent to metastatic disease after surgery (population 4)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Total patients eligible	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Total Number of patients treated [a]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Number of scripts dispensed [b]	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Estimated financial implications of retifanlimab						
Cost to PBS/RPBS less copayments	$[redacted]3	$[redacted]3	$[redacted]3	$[redacted]4	$[redacted]4	$[redacted]4
Estimated financial implications for carboplatin + paclitaxel						
Cost to PBS/RPBS less copayments [c]	0	0	0	0	0	0
Net financial implications						
Net cost to PBS/RPBS	$[redacted]3	$[redacted]3	$[redacted]3	$[redacted]4	$[redacted]4	$[redacted]4
Net cost to MBS	$[redacted]3	$[redacted]3	$[redacted]3	$[redacted]3	$[redacted]3	$[redacted]3
Net cost to health budget	$[redacted]3	$[redacted]3	$[redacted]3	$[redacted]4	$[redacted]4	$[redacted]4

Source: Tables 105, 106 and 110, p179 and 183 of the submission.

[a] Assumed [redacted]% uptake rate

[b] Assuming 9 scripts per patient as estimated by the submission.

[c] Carboplatin and paclitaxel costs were not included in the financial estimates as the submission assumed these costs would be equal if retifanlimab is or is not PBS listed.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$0 to < $10 million*

[4] *$10 million to < $20 million*

6.55 The submission estimated that the total cost to the PBS/RPBS of listing retifanlimab would be $10 million to < $20 million in Year 1, increasing to $10 million to < $20 million in Year 6, and a total of $50 million to < $60 million in the first 6 years of listing. DUSC considered that there is a great unmet clinical need in this population and as such there would likely be high uptake in this market. The PBAC considered the submission's estimated uptake rate, of [redacted]% was reasonable.

6.56 The DUSC and the PBAC noted additional uncertainties regarding the inputs used to estimate the number of eligible patients and retifanlimab uptake:

- The submission applied a linear extrapolation of AIHW data instead of using the published projections for anal cancer by the AIHW. Using the projected AIHW data increased the cost over six years by 5%;

- The assumed percentage of patients with SCAC as a proportion of all anal cancer (71.8%) may be underestimated as Pedersen 2025 reported a SCAC proportion of 75-95%. Assuming a SCAC proportion of 75% and 95% increased the cost over six years by 4% and 32%, respectively. DUSC considered the incidence of SCAC at diagnosis was likely underestimated;

6.57 Overall, DUSC believed the population structure aligned well with the indication, however the incidence estimates overall may be underestimated. The financial impact was sensitive to how the eligible population was defined, but it also showed that the estimates were reasonably stable within a predictable range. The impact could be larger if the assumptions included in the submission's sensitivity analyses were combined. DUSC advised that minor changes to the methods used to derive the utilisation and financial estimates and structure of the estimates model should be considered, including using the latest Australian Institute of Health and Welfare (AIHW) data to estimate the incident patients with anal cancer, and increasing the population of patients with anal cancer who have SCAC at diagnosis to 85%.

6.58 The Pre-PBAC response presented revised financial estimates (see Table 18) to align with the DUSC advice, whereby the projected number of patients with anal cancer was based on AIHW long-term cancer projections and the proportion of anal cancer cases with the SCAC subtype was equal to 85% (increased from 71.8%). Additionally, a retifanlimab price of $[redacted] per 500 mg vial was applied in line with the revised base case (paragraph 6.49). This resulted in an increased combined net financial impact to the PBS/RBS and MBS of $0 to < $10 million Year 1, increasing to $10 million to < $20 million in Year 6, and a total of $50 million to < $60 million in the first 6 years of listing.

Table 18 Pre-PBAC Revised financial estimates

	2026	2027	2028	2029	2030	2031
Estimated extent of use						
Total patients eligible	[redacted][1]	[redacted][1]	[redacted]	[redacted][1]	[redacted][1]	[redacted][1]
Total number of patients treated[a,c]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed[b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost to PBS/RPBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][4]	$[redacted][4]
Net cost to MBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to PBS/RPBS/MBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][4]	$[redacted][4]	$[redacted][4]

Source: Pre-PBAC response (from revised financial workbook)

[a] Assumed [redacted]% uptake rate.

[b] Assuming 9 scripts per patient as estimated by the submission.

[c] The pre-PBAC response used updated AIHW data from the Cancer data in Australia, Data - Australian Institute of Health and Welfare AIHW data tables CDIA 2025: Book 1e.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$0 to < $10 million*

[4] *$10 million to < $20 million*

Financial Management – Risk Sharing Arrangements

6.59 The submission claimed that as the proposed restriction criteria for retifanlimab for the treatment of SCAC is well defined, this will help to ensure only suitable patients are treated and will cap the duration of treatment with retifanlimab, mitigating leakage and providing greater certainty in terms of the financial impact of listing retifanlimab for SCAC. Consequently, the submission claimed that a Risk Sharing Arrangement was not required for retifanlimab in this setting. The evaluation considered that while the proposed restriction would allow use of retifanlimab initiated in combination with CP, there is a potential risk of retifanlimab being used as monotherapy in the 2L setting.

6.60 DUSC considered that there would likely be limited extent of usage beyond the requested restriction.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for retifanlimab for the treatment, in combination with carboplatin and paclitaxel (CP), of inoperable locally recurrent or metastatic squamous cell anal carcinoma (SCAC) not previously treated with systemic chemotherapy. The PBAC was of a mind to recommend retifanlimab pending the provision of a positive TGA Delegate's Overview, based on superior efficacy to CP alone as demonstrated in a double blind, randomised controlled trial (RCT). The PBAC considered that retifanlimab would be acceptably cost-effective at a price resulting in an incremental cost effectiveness ratio (ICER) of less than $75,000 to < $95,000 per quality adjusted life year (QALY), with updated inputs to the economic model including a 10-year time horizon and using the intention-to-treat (ITT) results for overall survival (OS).

7.2 The PBAC was satisfied that retifanlimab in combination with CP provides, for some patients, a significant improvement in efficacy over CP alone.

7.3 The PBAC considered there was a high clinical need for new treatments for SCAC, as response rates to standard of care (SOC) chemotherapy (e.g. carboplatin and paclitaxel) are moderate, and disease progression is inevitable. The PBAC noted that SCAC is a rare cancer, with increased prevalence in people with HIV.

7.4 The PBAC considered that it is appropriate for the restriction to be Authority required (STREAMLINED), as requested in the submission. The PBAC recommended that the clinical criteria, "Patients must not have received prior systemic therapy" should include "… in the inoperable locally recurrent or metastatic setting," as patients may have received chemotherapy with radiation for localised disease.

7.5 The PBAC considered that the submission's proposed place in therapy was consistent with the supporting clinical trial (POD1UM-303), the National Comprehensive Cancer

Network (NCCN), and European Society for Medical Oncology (ESMO) clinical guidelines.

7.6 The PBAC considered that the submission's proposed comparator, CP, was appropriate, noting that CP is the current standard of care for the 1L treatment of advanced or metastatic SCAC in the NCCN and ESMO guidelines. The PBAC recalled that, at its September 2025 intracycle meeting, it had recommended a multi-indication (broad) listing for nivolumab and ipilimumab in advanced or metastatic cancers, which would include SCAC, however the Committee also noted that nivolumab is not currently TGA registered for this indication.

7.7 The submission was based on one head-to-head double-blind RCT (POD1UM-303) comparing retifanlimab + CP to placebo + CP (N=308) in which patients received a maximum of one year of treatment. After disease progression, patients randomised to placebo + CP could elect to receive open label retifanlimab monotherapy for up to one year. The PBAC considered that the trial was well designed and at low risk of bias during the double-blind period (until progression) and acknowledged the challenges in conducting an RCT in this rare condition. The PBAC considered that the trial population and processes of care were representative of care in Australia.

7.8 The PBAC considered that there was strong evidence to support a PFS benefit in POD1UM-303, with a PFS hazard ratio (HR) of 0.63 (95% CI: 0.47, 0.84). The PBAC considered that an OS benefit was likely, noting an OS HR of 0.70 (95% CI: 0.49, 1.01; p = 0.0273); however the magnitude was uncertain due to relatively immature OS data (only 41% of patients had died), and potential confounding due to 45% of patients randomised to the placebo arm crossing over to receive retifanlimab monotherapy after disease progression. The PBAC noted that the submission used the rank-preserving structural failure time (RPSFT) and inverse probability of censoring weighting (IPCW) models to conduct *post hoc* adjustments for treatment switching (RPSFT: OS HR = 0.63, 95% CI 0.44, 0.90, p=0.0055; IPCW: OS HR = 0.61, 95% CI 0.40, 0.95, p=0.0063), which the submission claimed were statistically significant (paragraphs 6.14 - 6.16). However, the PBAC considered that the RPFST and IPCW OS analyses were highly uncertain and not well supported. This was because of the relatively short duration of use of second-line (2L) retifanlimab monotherapy, and because several of the assumptions underpinning the crossover adjustments were unlikely to hold. These included the following assumptions: constant treatment effect (because the OS benefit of retifanlimab in 2L as monotherapy is likely smaller than in 1L in combination with CP); that all prognostic factors at the time of disease progression were accounted for; and that there were no other unobserved confounders (paragraph 6.17). The PBAC considered that the ITT OS results were more informative than the results adjusted for crossover. Overall, the PBAC considered that the claim of superior comparative effectiveness was reasonable, but the magnitude of OS benefit remained uncertain.

7.9 The PBAC noted that adverse events (AEs) were more commonly observed to occur in the retifanlimab + CP arm of POD1UM-303 including higher rates of

retifanlimab/placebo-related TEAEs (RR 1.15; 95% CI 1.04, 1.28), serious retifanlimab/placebo-related TEAEs (RR 2.47; 95% CI 1.23, 4.96) and retifanlimab/placebo treatment discontinuation due to a TEAE (RR 4.19; 95% CI 1.44, 12.18) compared to the placebo + CP arm. The PBAC considered that the additional toxicity was consistent with that observed with other immunotherapy agents. The PBAC noted low completion rates for health-related quality of life (HRQoL) patient-reported outcomes assessed in POD1UM-303 (paragraphs 6.21 - 6.22). Overall, the PBAC considered the claim of inferior comparative safety was reasonable.

7.10 The submission presented a cost-utility analysis based on the POD1UM-303 trial, and revisions were proposed in the pre-PBAC response to address some of the ESC's key concerns. While the submission's base case used the OS results that were adjusted for cross-over (using the RPSFT method), this was revised to the ITT OS results in the pre-PBAC response. Further, the pre-PBAC response adjusted the time horizon from 15 years to 10 years (maintaining no convergence) and included a reduction in the proposed vial price. The PBAC noted that the pre-PBAC response's revised model estimated an incremental cost effectiveness ratio (ICER) of $75,000 to < $95,000 per QALY. The PBAC considered that the changes proposed in the pre-PBAC response were appropriate, although noted that the ICER remained potentially overestimated due to the assumptions regarding continued benefit over the model time horizon (see paragraphs 6.35 and 6.48) and the time point at which the model switches from Kaplan Meier (KM) data to parametric extrapolation (see paragraphs 6.39 - 6.41 and 6.48). In this context, and noting the rarity of the disease and the available evidence base, the PBAC considered that retifanlimab would be acceptably cost effective with a price reduction resulting in an ICER less than $75,000 to < $95,000 per QALY, using the inputs from the pre-PBAC response's respecified base case.

7.11 The submission used an epidemiological approach to estimate the size of the eligible patient population. The PBAC considered that the financial estimates presented in the submission were likely underestimated and that the following two changes were required: the published AIHW projection data should be used to derive incidence of anal cancer; and the proportion of SCAC at diagnosis should be increased from 72% to 85% (paragraph 6.57), as applied in the Pre-PBAC response (paragraph 6.58). The PBAC considered that the estimates would also need to be updated with the revised price, as per paragraph 7.10.

7.12 The PBAC noted that this submission is not eligible for an Independent Review as it was deferred.

Outcome:
Deferred

8 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.