6.02 ENFORTUMAB VEDOTIN, Powder for I.V. infusion 20 mg, Powder for I.V. infusion 30mg, Padcev®, ASTELLAS PHARMA AUSTRALIA PTY LTD.

1 Purpose of submission

1.1 The Category 2 submission requested Section 100 (Efficient Funding of Chemotherapy Program) Authority Required (STREAMLINED) listing for enfortumab vedotin in combination with pembrolizumab (EV+PEM) for the first line treatment of locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer (la/mUC).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus platinum based chemotherapy with gemcitabine (Plat+Gem).

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

Component	Description
Population	Patients with previously untreated locally advanced or metastatic urothelial cancer
Intervention	Enfortumab vedotin 1.25 mg/kg IV on Days 1 and 8 with pembrolizumab 200 mg IV on Day 1 of each 3-week cycle, for up to 35 cycles for PEM (EV+PEM)
Comparator	Platinum-based chemotherapy (gemcitabine 1000 mg/m^2 IV on Days 1 and 8 with either cisplatin 70 mg/m^2 IV or carboplatin AUC 4.5 IV on Day 1 of each 3-week cycle) for up to 6 cycles (Plat+Gem)
Outcomes	Progression-free survival, overall survival, objective response rate, duration of response, patient-reported outcomes, safety
Clinical claim	In patients with previously untreated locally advanced or metastatic urothelial cancer, EV+PEM is superior to Plat+Gem in terms of effectiveness and superior in terms of safety

Source: Table 1-1, p28 of the submission.
AUC = area under the curve; EV = enfortumab vedotin; GEM = gemcitabine; IV = intravenous; PEM = pembrolizumab; plat = platinum.
Note: EV is given until disease progression.

2 Background

Registration status

2.1 The submission was made under TGA/PBAC Parallel Process. EV was submitted for the treatment of adult patients with la/mUC on 24 January 2024. At the time of PBAC consideration, the TGA Delegate's Overview was available. The Delegate stated they were in a position to approve EV, in combination with pembrolizumab, for the treatment of adult patients with la/mUC who have not previously received systemic therapy for mUC.

2.2 Pembrolizumab was also submitted to the TGA in February 2024 for the treatment of patients with la/mUC.

2.3 EV is currently registered in the ARTG for the treatment of adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor.

2.4 Pembrolizumab is listed on the ARTG for numerous indications. The current indications of relevance to urothelial cancer are:

- Monotherapy for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy
- Monotherapy for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy
- Treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in-situ (CIS) with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy.

2.5 On 3 April, 2023, the U.S. Food and Drug Administration (FDA) granted accelerated approval to EV+PEM for patients with la/mUC who are ineligible for cisplatin-containing chemotherapy. Following the evaluation of primary results from the EV-302 trial, EV+PEM was approved by the FDA on 15 December 2023 for the treatment of adult patients with la/mUC, without restriction by cisplatin eligibility.

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

3 Requested listing

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

Enfortumab vedotin

MEDICINAL PRODUCT Form	**Dispensed Price Max Amt**	**PBS item code**	**Max. Amount**	**№.of Rpts**
ENFORTUMAB VEDOTIN Injection	$[redacted] published price (public) $[redacted] published price (private)	NEW (Public) NEW (Private)	125mg	7
Available brands				
Padcev (enfortumab vedotin 30 mg injection, 1 vial)				
Padcev *(enfortumab vedotin 20 mg injection, 1 vial)*				
Restriction Summary [new] / Treatment of Concept: [new]				
	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: n/a
		Severity: Locally advanced (Stage III) or metastatic (Stage IV)
		Condition: Urothelial cancer
		Indication: Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
		Treatment Phase: ~~Initial and continuing treatment~~
		Clinical criteria:
		Patient must not have received prior systemic therapy for this condition, with the exception of neoadjuvant/adjuvant chemotherapy.
		AND
		Clinical criteria:
		Patient must have/have had a WHO performance status score of no greater than 2 at treatment initiation with this drug.
		Treatment criteria:
		Patient must be undergoing combination therapy consisting of *no more than 24 months of*: (i) enfortumab vedotin, (ii) pembrolizumab; OR
		Patient must be undergoing monotherapy with this drug after *exceeding a total of* ~~receiving no longer than~~ 24 *cumulative* months of ~~the~~ combination therapy *consisting of: (i) enfortumab vedotin, (ii) pembrolizumab, from the first administered dose, once in a lifetime* ~~mentioned above~~; OR
		Patient must be undergoing monotherapy with this drug due to a contraindication/intolerance to pembrolizumab, requiring temporary/permanent discontinuation; document the details in the patient's medical records.
		AND
		Treatment criteria:
		Patient must be undergoing treatment with this drug for the first time; OR
		Patient must be undergoing continuing treatment with this drug, with each of the following being true: (i) all other PBS eligibility criteria in this restriction are met, (ii) disease progression is absent.
Restriction Summary [new] / Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (STREAMLINED) [new]
		Indication: Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
		Treatment Phase: Transitioning from non-PBS to PBS subsided treatment – 'Grandfather' arrangement
		Clinical criteria:
		Patient must have received non-PBS-subsidised treatment with this drug for this indication prior to [date of PBS listing],
		AND
		Clinical criteria:
		Patient must have/have had a WHO performance status score of no greater than 2 prior to initiation of non-PBS-subsidised treatment with this drug for this condition,
		AND
		Clinical criteria:
		Patient must not have developed disease progression while being treated with this drug for this condition.
		Treatment criteria:

	Patient must be undergoing combination therapy consisting of *no more than 24 months of*: (i) enfortumab vedotin, (ii) pembrolizumab; OR
	Patient must be undergoing monotherapy with this drug after *exceeding a total of* ~~receiving no longer than~~ 24 *cumulative* months of ~~the~~ combination therapy *consisting of: (i) enfortumab vedotin, (ii) pembrolizumab, from the first administered dose, once in a lifetime* ~~mentioned above~~; OR
	Patient must be undergoing monotherapy with this drug due to a contraindication/intolerance to pembrolizumab, requiring temporary/permanent discontinuation; document the details in the patient's medical records;
	Administrative Advice: *Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Initial and Continuing treatment' criteria.*
	Administrative Advice: *This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.*

Pembrolizumab

MEDICINAL PRODUCT Form	Dispensed Price for Max. Qty	PBS item code	Max. Amount	№.of Rpts
PEMBROLIZUMAB Injection	$7,737.63 published price (public) $7,889.37 published price (private)	NEW (Public) NEW (Private)	*200* ~~400~~mg	3

Available brands	
Keytruda (pembrolizumab 100 mg/4 mL injection, 4 mL vial)	
Restriction Summary [new] / Treatment of Concept: [new]	
	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.*
	Administrative Advice: *In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.*
	Episodicity: n/a
	Severity: Locally advanced (Stage III) or metastatic (Stage IV)
	Condition: Urothelial cancer
	Indication: Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
	Treatment Phase: ~~Initial and continuing treatment~~
	Clinical criteria:
	Patient must not have received prior systemic therapy for this condition, with the exception of neoadjuvant/adjuvant chemotherapy,
	AND
	Clinical criteria:
	Patient must have/have had a WHO performance status score of no greater than 2 at treatment initiation with this drug.
	Treatment criteria:
	Patient must be undergoing combination therapy consisting of *no more than 24 months of*: (i) enfortumab vedotin, (ii) pembrolizumab; OR

	Patient must be undergoing monotherapy with this drug due to intolerance to enfortumab vedotin, requiring temporary/permanent discontinuation; document the details in the patient's medical records,
	AND
	Treatment criteria:
	Patient must not be undergoing *continuous PBS-subsidised* treatment *where this benefit is extending treatment beyond* ~~with this drug beyond~~ 24 *cumulative* months from the first administered dose, *once in a lifetime.*
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this drug for the first time; OR
31068	Patient must be undergoing continuing treatment with this drug, with each of the following being true: (i) all other PBS eligibility criteria in this restriction are met, (ii) disease progression is absent.
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (STREAMLINED) [new]
	Indication: Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
	Treatment Phase: Transitioning from non-PBS to PBS subsided treatment – 'Grandfather' arrangement
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this indication prior to [date of PBS listing],
	AND
	Clinical criteria:
	Patient must have/have had a WHO performance status score of no greater than 2 prior to initiation of non-PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition.
	Treatment criteria:
	Patient must be undergoing combination therapy consisting of *no more than 24 months of*: (i) enfortumab vedotin, (ii) pembrolizumab; OR
	Patient must be undergoing monotherapy with this drug due to intolerance to enfortumab vedotin, requiring temporary/permanent discontinuation; document the details in the patient's medical records,
	AND
	Treatment Criteria:
	Patient must not be undergoing treatment with this drug beyond 24 *cumulative* months from the first administered dose, *once in a lifetime*.
	Administrative Advice: *Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Initial and Continuing treatment' criteria.*
	Administrative Advice: *This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.*

3.2 As EV and PEM are marketed by two separate companies, an effective price for each product, as well as the combination, was not proposed. The submission states that it is anticipated that the sponsor of each product will undergo negotiation with the

Department following a positive recommendation to determine an appropriate effective price for each drug.

3.3 The proposed PBS restriction aligns with the proposed TGA indication. The clinical criteria are consistent with the EV-302 trial in that patients with an ECOG performance status score of 0, 1 or 2 were eligible as were patients who had not received prior systemic therapy for la/mUC with the exception of neoadjuvant chemotherapy or adjuvant chemotherapy. However, in the EV-302 trial, patients who had received neoadjuvant chemotherapy were only eligible if they had recurrence more than 12 months from completion of therapy. In addition, patients who had received adjuvant chemotherapy were eligible if it was following cystectomy with recurrence more than 12 months from completion of therapy. The clinical criteria referring to neoadjuvant/adjuvant chemotherapy does not specify that recurrence needs to be more than 12 months from completion of therapy. The PBAC noted 96% of patients in EV-302 had a performance status of 0 or 1 and considered this might be higher than would be observed in the Australian treatment setting.

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

4 Population and disease

4.1 Urothelial carcinomas are cancers which arise from the urothelial cells lining the bladder, ureters, urethra, and renal pelvis[1]. In its locally advanced stage, the cancer has extended beyond the primary site to nearby tissues, organs, or lymph nodes, while in the metastatic stage, it has spread to distant parts of the body, such as the lungs, liver, or bones[2]. La/mUC is particularly challenging to manage due to its aggressive progression and resistance to conventional treatments[3].

4.2 Bladder cancer, primarily urothelial carcinoma, is the ninth most common cancer in Australia. Each year, around 3,000 new cases are diagnosed, with the disease predominantly affecting older adults, particularly those over the age of 65[4,5]. The incidence is significantly higher in men, with a male-to-female ratio of approximately 3:1. Risk factors include smoking (the most significant risk factor), exposure to certain chemicals (such as those used in the dye and rubber industries), and chronic bladder inflammation[6]. Although the incidence of bladder cancer has been stable or slightly decreasing, the prognosis for those with la/mUC remains poor.

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[1] Abou El-Ghar ME, Badawy MA, El-Diasty TA (2018). Bladder and Upper Urinary Tract Urothelial Cancer. In: Akata D, Papanikolaou N, editors. Diffusion Weighted Imaging of the Genitourinary System: Techniques and Clinical Applications. Cham: Springer International Publishing; p. 73-104.

[2] Kobayashi T. (2016). Understanding the biology of urothelial cancer metastasis. *Asian J Urol*. Oct;3(4):211-22.

[3] Stecca C, Abdeljalil O, Sridhar SS. (2021). Metastatic Urothelial Cancer: a rapidly changing treatment landscape. *Ther Adv Med Oncol*;13:17588359211047352.

[4] Cancer Australia (2024). https://www.canceraustralia.gov.au/cancer-types/bladder-cancer/statistics.

[5] Australian Institute of Health, Welfare (2024). Cancer data in Australia. Canberra: AIHW2024.

[6] Shadab R, Nerli RB, Bidi SR, Ghagane SC. (2023). Risk Factors for Bladder Cancer: Results of a Survey of Hospital Patients. J Cancer Allied Spec. 9(1):485

4.3 For patients with localised urothelial cancer (confined to the bladder), the five-year survival rate is relatively favourable, typically exceeding 70-80%[7]. However, survival rates with locally advanced disease are around 30%-50% and patients with metastatic disease have a 5-year survival rate of approximately 5-15%[8].

4.4 The proposed clinical management algorithm would place EV+PEM as the preferred first line treatment for la/mUC. Patients who cannot receive EV+PEM would be able to receive the current standard of care (SoC) instead. Upon progression on EV+PEM, patients would be treated with Plat+Gem. The ESC noted the NCCN Clinical Practice Guidelines[9] include EV+PEM as the preferred regimen for all la/mUC patients.

4.5 EV is an antibody drug conjugate comprising an IgG1-kappa antibody targeted to nectin-4 and the microtubule-disrupting agent, monomethyl auristatin E (MMAE)[10]. Because nectin-4 displays limited expression in normal tissues compared with cancerous tissues[11], this allows EV to target the delivery of MMAE to cancerous cells.

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

5 Comparator

5.1 The submission nominated SoC consisting of Plat+Gem as the comparator. The main arguments provided in support of this nomination were that Plat+Gem is the recommended SoC for the first line treatment of la/mUC in Australia.

5.2 Although the nominated comparator is reasonable, patients who do not progress on Plat+Gem are eligible to receive avelumab maintenance therapy in Australia. As EV+PEM is administered until disease progression, avelumab maintenance therapy could be included as a component of the main comparator. This would create two comparator populations: Those who progress while on platinum-based chemotherapy and those who do not progress and receive avelumab maintenance therapy. It should be noted that although the submission did not include avelumab in the main comparator, approximately 30% of the patients in the key EV-302 trial did receive subsequent avelumab maintenance therapy.

5.3 Nivolumab in combination with cisplatin (Nivo+Cis) chemotherapy should be considered as a near market comparator. Nivo+Cis was submitted to the PBAC for consideration at the November 2024 PBAC meeting for the first line treatment of

[7] Ripoll J, Ramos M, Montaño J, Pons J, Ameijide A, Franch P. (2021). Cancer-specific survival by stage of bladder cancer and factors collected by Mallorca Cancer Registry associated to survival. *BMC Cancer*;21(1):676.
[8] Gurney H, Clay TD, Oliveira N, Wong S, Tran B, Harris C. (2023). Systemic treatment of advanced and metastatic urothelial cancer: The landscape in Australia. *Asia-Pacific Journal of Clinical Oncology*.19(6):585-95.
[9] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 4.2024 (May 9, 2024).
[10] Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee JL, et al. (2021). Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. *N Engl J Med*. Mar 25;384(12):1125-35.
[11] Heath EI, Rosenberg JE. (2021), The biology and rationale of targeting nectin-4 in urothelial carcinoma. *Nat Rev Urol*. Feb;18(2):93-103.

unresectable or metastatic urothelial cancer[12]. The Pre-Sub-Committee Response (PSCR) noted that Nivo+Cis will only be suitable for patients who are cisplatin-eligible and stated that this is expected to represent only half of the la/mUC population (remainder unable to receive cisplatin due to poor performance status, renal impairment, or other comorbidities). The ESC agreed with the PSCR argument that Nivo+Cis would not be a relevant comparator for patients ineligible for cisplatin.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (11), health care professionals (4) and organisations (3) via the Consumer Comments facility on the PBS website. The input from individuals who have used this medicine for their own health along with input from their partners or family members described benefits of EV+PEM treatment including reductions in tumour size and cancer-related symptoms along with improvements in quality of life. The input from these individuals also described side effects experienced during EV+PEM treatment, including diarrhoea, fatigue, severe itching, body hair loss, brain fog, skin blistering and neuropathy in feet and fingertips. Access issues due to current prohibitive costs were also highlighted. The input from health care professionals highlighted the major incremental benefit in overall survival and high response rates reported for EV+PEM in this poor prognosis cancer. Health care professional input also described the lack of effective treatment options for patients who are ineligible for platinum based chemotherapy. BEAT Bladder Cancer Australia described what it is like to live with la/mUC given its high recurrence and low survival rates and the impact on a patients mental health. Consistent with the input from Rare Cancers Australia, the input described the advantages of such therapy as patients living longer with improvements in quality of life which would be highly beneficial to the patient and their supporting carer/family.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the EV+PEM submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the EV-302 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for EV+PEM, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement),[13] based on a

[12] November 2024 PBAC meeting agenda. Pharmaceutical Benefits Scheme (PBS) | November 2024 PBAC Meeting

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

comparison with Plat+Gem.

Clinical trials

6.4 The submission was based on one head-to-head trial comparing EV+PEM versus Plat+Gem in previously untreated la/mUC patients (n=886), the EV-302 trial.

6.5 Details of the trial presented in the submission are provided in Table 2.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
EV-302 NCT04223856	Powles, T., Valderrama, B. P., Gupta, S., Bedke, J., Kikuchi, E., Hoffman-Censits, J., Iyer, G., Vulsteke, C. A.-O., Park, S. H., Shin, S. J., Castellano, D., Fornarini, G., Li, J. R., Gümüş, M., Mar, N., Loriot, Y., Fléchon, A., Duran, I., Drakaki, A., Narayanan, S., Yu, X., Gorla, S., Moreno, B., Van der Heijden, M. S. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer	*The New England Journal of Medicine* 2024; 390(10): 875-888.
	Van Der Heijden, M. S., Powles, T., Gupta, S., Bedke, J., Kikuchi, E., De Wit, R., Galsky, M. D., Duran, I., Necchi, A., Retz, M., Yu, E. Y., Hoffman-Censits, J. H., Iyer, G., Park, S. H., Su, W.-P., Parmar, H., Guan, X., Gorla, S. R., Moreno, B., Valderrama, B. P. Enfortumab vedotin (EV) in combination with pembrolizumab (P) versus chemotherapy in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC): Subgroup analyses results from EV-302, a phase 3 global study.	*Journal of Clinical Oncology* 2024; 42(4_suppl)
	Powles, T. B., Perez Valderrama, B., Gupta, S., Bedke, J., Kikuchi, E., Hoffman-Censits, J., Iyer, G., Vulsteke, C., Park, S. H., Shin, S. J., Castellano Gauna, D. E., Fornarini, G., Li, J. R., Gumus, M., Mar, N., Narayanan, S., Yu, X., Gorla, S., Moreno, B., Van der Heijden, M. S. 211MO EV-302/KEYNOTE-A39: Open-label, randomized phase III study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (Chemo) in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC).	*Annals of Oncology* 2023; 34: S1557-S1558
	Powles, T. B., Perez Valderrama, B., Gupta, S., Bedke, J., Kikuchi, E., Hoffman-Censits, J., Iyer, G., Vulsteke, C., Park, S. H., Shin, S. J., Castellano Gauna, D. E., Fornarini, G., Li, J. R., Gumus, M., Mar, N., Narayanan, S., Yu, X., Gorla, S., Moreno, B. M. S., Van der Heijden, M. S. LBA6 EV-302/KEYNOTE-A39: Open-label, randomized phase III study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (Chemo) in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC)	*Annals of Oncology* 2023; 34: S1340
	Van Der Heijden, M. S., Gupta, S., Galsky, M. D., Derleth, C. L., Lee, S., Kataria, R. S., Powles, T. Study EV-302: A two-arm, open-label, randomized controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy in previously untreated advanced urothelial carcinoma (aUC) (trial in progress)."	*Journal of Clinical Oncology* 2022; 40(6_suppl): TPS589-TPS589.
	Van der Heijden, M. S., Gupta, S., Galsky, M. D., Derleth, C., Steinberg, J., Kataria, R., Powles, T. B. 798TiP Study EV-302: A 3-arm, open-label, randomized phase III study of enfortumab vedotin plus pembrolizumab and/or chemotherapy, versus chemotherapy alone, in untreated locally advanced or metastatic urothelial cancer	*Annals of Oncology* 2020; 31: S605-S606.
	Astellas Pharma. Enfortumab Vedotin and Pembrolizumab vs. Chemotherapy Alone in Untreated Locally Advanced or Metastatic Urothelial Cancer. ClinicalTrials.gov identifier: NCT04223856. https://clinicaltrials.gov/ct2/show/NCT04223856	2023

Source: Table 2-2, p48 of the submission.
EV = Enfortumab vedotin; la/mUC = Locally advanced or metastatic urothelial cancer

6.6 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	Outcomes	Use in modelled evaluation
EV+PEM vs. Plat+Gem						
EV-302	886	R, OL	Low	Previously untreated la/mUC	PFS, OS, ORR, DOR PRO, safety	OS, PFS

Source: Table 2-3, p51, Table 2-4, p53, and Table 2-11, pp63-64 of the submission.
DOR = Duration of response; EV = Enfortumab vedotin; Gem = Gemcitabine; OL = open label; ORR = Objective response rate; OS = Overall survival; PEM = Pembrolizumab; PF = Progression-free; PFS = Progression-free survival; PRO = Patient-reported outcome; Plat = Platinum-based chemotherapy; R = randomised; la/mUC = Locally advanced or metastatic urothelial cancer

6.7 Overall, the risk of bias was considered low in the EV-302 trial except for outcomes with subjective elements such as patient reported outcomes (PROs) and patient reported adverse events (AEs) due to the trial being open label. The risk of bias for the primary efficacy outcome of progression free survival (PFS) was minimised using blinded independent central review (BICR).

6.8 Table 4 displays the subsequent anti-cancer therapies in the EV-302 trial. In the Plat+Gem arm, 30.4% of patients received avelumab maintenance therapy. The ESC noted that overall response rates of 54.3%[14] and 56.1%[15] were reported for the gemcitabine + cisplatin and gemcitabine + carboplatin arms respectively in the original trials for these agents in advanced or metastatic bladder cancer. Noting that patients who do not progress on Plat+Gem are eligible to receive avelumab maintenance therapy in Australia, the ESC considered the proportion of patients who received avelumab maintenance therapy in EV-302 is likely to be less than what is observed in the Australian clinical setting. Outside of use as maintenance therapy, the ESC also noted that the use of subsequent PD-(L)1 therapies was 26.4%. The pre-PBAC response stated that patients receiving maintenance avelumab reflected over 50% of patient who were progression free after chemotherapy.

[14] von der Maase, H., Hansen, S. W., Roberts, J. T., Dogliotti, L., Oliver, T., Moore, M. J., et al. (2000). Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *Journal of clinical oncology*, *18*(17), 3068–3077.

[15] Nogué-Aliguer, M., Carles, J., Arrivi, A., Juan, O., Alonso, L., Font, A., Mellado, B., Garrido, P., Sáenz, A., & Spanish Cooperative Group (2003). Gemcitabine and carboplatin in advanced transitional cell carcinoma of the urinary tract: an alternative therapy. *Cancer*, *97*(9), 2180–2186.

Table 4: Subsequent anticancer therapy (ITT) in EV-302 trial

	EV+PEM N=442	Plat+Gem N=444
Any subsequent therapy	140 (31.7)	313 (70.5)
First subsequent systemic therapy, n (%)		
Platinum-based therapy	110 (24.9)	17 (3.8)
Cisplatin based	53 (12.0)	8 (1.8)
Carboplatin based	56 (12.7)	8 (1.8)
Other	1 (0.2)	1 (0.2)
Maintenance PD-1/L1 inhibitor	0	143 (32.2)
Avelumab	0	135 (30.4)
Pembrolizumab	0	7 (1.6)
Other PD-1/L1 inhibitor-containing therapy	7 (1.6)	117 (26.4)
Other	11 (2.5)	17 (3.8)
Enfortumab vedotin	3 (0.7)	3 (0.7)
Second and beyond subsequent systemic therapy, n (%)		
Platinum-based therapy	8 (1.8)	10 (2.3)
Maintenance PD-1/L1 inhibitor	8 (1.8)	7 (1.6)
Other PD-1/L1 inhibitor containing therapy	7 (1.6)	12 (2.7)
Other	24 (5.4)	82 (18.5)
Enfortumab vedotin	0	54 (12.2)

Source: Table 2-10, p62 of the submission.
EV = Enfortumab vedotin; Gem = Gemcitabine; ITT = Intention to treat; PD-1 = Programmed cell death protein 1; PEM = Pembrolizumab; Plat = Platinum-based chemotherapy.

6.9 Minimal clinically important differences were not specified for any of the outcomes. The submission did note that the PBAC has previously considered a PFS gain of 1.7 months as "small" in their evaluation of avelumab for maintenance treatment of la/mUC following first-line platinum-based chemotherapy (paragraph 7.5, avelumab, Public Summary Document [PSD], March 2021 PBAC meeting). Additionally, the submission noted that a separate evaluation of pembrolizumab, which was recommended for second-line treatment of la/mUC, the PBAC considered that the claim of superior effectiveness was adequately supported by the OS data which showed a gain of 2.9 months (paragraph 6.30, pembrolizumab PSD, November 2017 PBAC meeting).

Comparative effectiveness

6.10 In the EV-302 trial, the primary efficacy outcomes were PFS by BICR and overall survival (OS) in the intention to treat population (ITT). The data cut-off (DCO) was 8 August 2023. At this DCO the median duration of follow-up was 17.2 months across both arms.

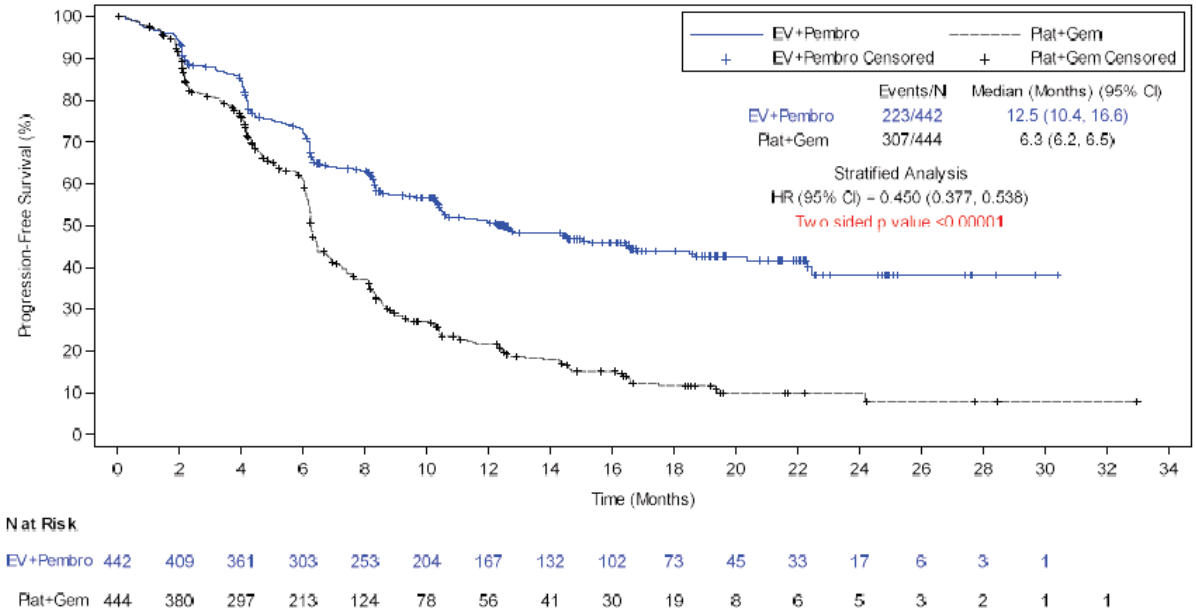
6.11 Table 5 summarises the survival outcomes in the EV-302 trial. Figure 1 shows the Kaplan-Meier (KM) plot for PFS by BICR and Figure 2 shows the KM plot for OS.

Table 5: Summary of survival outcomes in EV-302 (ITT population)

	EV+PEM n/N (%)	Plat+GEM n/N (%)	Absolute difference	HR (95% CI)
Progression-free survival by BICR				
Patients with event	223/442 (50.5%)	307/444 (69.1%)	-	-
Median PFS, months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)	6.2	**0.45 (0.38, 0.54)**
PFS rate (%) at 6 months (95% CI)	72.8 (68.3, 76.8)	60.7 (55.7, 65.4)	12.1 [a]	-
PFS rate (%) at 12 months (95% CI)	50.7 (45.6, 55.5)	21.6 (17.2, 26.2)	29.1 [a]	-
PFS rate (%) at 18 months (95% CI)	43.9 (38.5, 49.1)	11.7 (8.0, 16.1)	32.3 [a]	-
Overall survival				
Number of deaths	133/422 (30.1%)	226/444 (50.9%)	-	-
Median OS, months (95% CI)	31.5 (25.4, NR)	16.1 (13.9, 18.3)	15.4	**0.47 (0.38, 0.58)**
OS rate (%) at 6 months (95% CI)	90.2 (87.0, 92.6)	81.9 (77.9, 85.2)	8.3 [a]	-
OS rate (%) at 12 months (95% CI)	78.2 (73.9, 81.9)	61.4 (56.6, 65.9)	16.8 [a]	-
OS rate (%) at 18 months (95% CI)	69.5 (64.4, 74.1)	44.7 (39.2, 50.1)	24.8 [a]	-

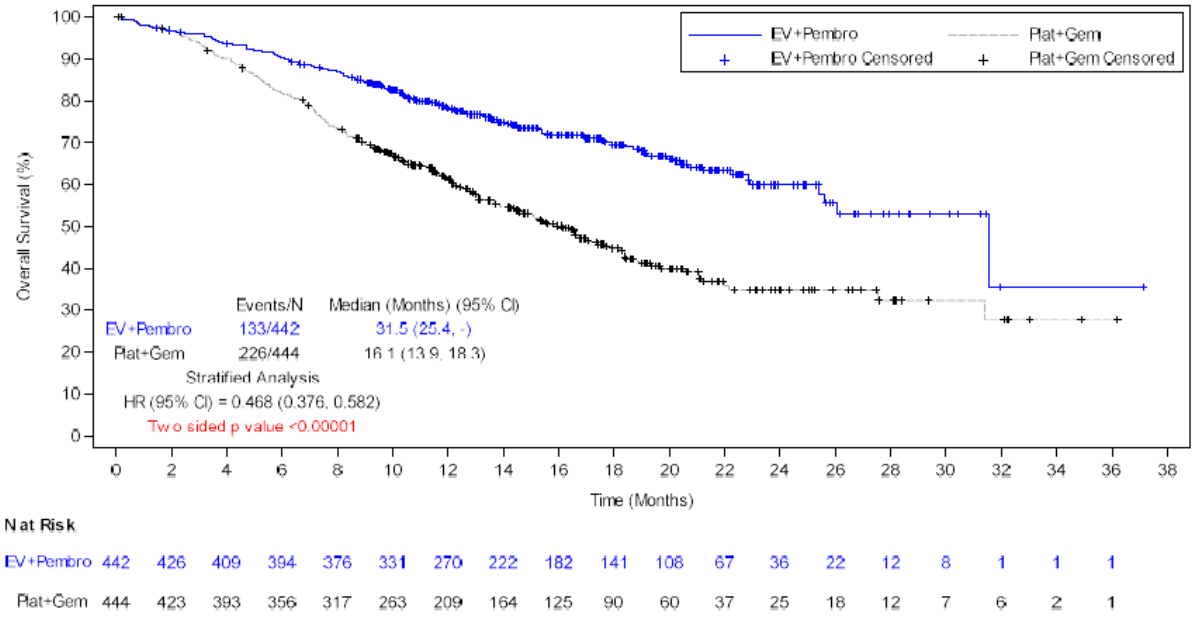
Source: Table 2-12, p66 and Table 2-13, p68 of the submission.
BICR = blinded independent central review; CI = confidence interval; EV+PEM = enfortumab vedotin with pembrolizumab; HR = hazard ratio; ITT = intention to treat population; OS = overall survival; PFS = progression free survival; Plat+GEM = platinum containing chemotherapy with gemcitabine; n = number of patients who progressed or died; N = number of patients in the arm; NR = not reached.
Bold = statistically significant
[a] calculated during the evaluation.

Figure 1: KM plot of PFS by BICR in EV-302 (ITT)



Source: Figure 2-4, p66 of the submission.
BICR = blinded independent central review; CI = confidence interval; EV+Pembro = enfortumab vedotin with pembrolizumab; HR = hazard ratio; ITT = intention to treat population; PFS = progression free survival; KM = Kaplan-Meier; Plat+GEM = platinum containing chemotherapy with gemcitabine

Figure 2: KM-plot of OS in EV-302 (ITT)



Source: Figure 2-6, p69 of the submission.
CI = confidence interval; EV+Pembro = enfortumab vedotin with pembrolizumab; HR = hazard ratio; ITT = intention to treat population; OS = overall survival; KM = Kaplan-Meier; Plat+GEM = platinum containing chemotherapy with gemcitabine.

6.12 For PFS in the ITT population, at a median follow-up of 17.2 months, there were 223 PFS events reported in the EV+PEM arm and 307 in the Plat+Gem arm. EV+PEM demonstrated a statistically significant improvement in PFS compared to Plat+Gem, with a 55% reduction in the risk of disease progression or death (HR=0.45; 95% CI: 0.38, 0.54; 2-sided p-value <0.00001). The median PFS in the EV+PEM arm was 12.5 months compared to 6.3 months in the Plat+Gem arm, corresponding to an incremental median PFS benefit of 6.2 months.

6.13 For OS in the ITT population, 30.1% of patients in the EV+PEM arm and 50.9% of patients in the Plat+Gem arm had died as of the 8 August 2023 DCO. A statistically significant reduction in the risk of death of 53.2% was observed in the EV+PEM arm compared to the Plat+Gem arm (HR=0.47; 95% CI: 0.38, 0.58; 2-sided p-value <0.00001). The median OS in the EV+PEM arm was 31.5 months compared to 16.1 months in the Plat+Gem arm, corresponding to an incremental median OS benefit of 15.4 months.

6.14 Although the OS data for EV+PEM presented in the submission shows a median OS of 31.5 months with a lower bound of the 95% confidence interval (CI) of 25.4 months, it should be noted that the upper bound of the 95% CI has yet to be reached. The median OS may change with more mature data.

6.15 The benefit in PFS and OS was demonstrated in almost all prespecified subgroups including age (<65 and ≥ 65), PD-L1 expression (Low and High), and Cisplatin eligibility (eligible and ineligible).

6.16 A subgroup analysis on the impact of maintenance therapy with avelumab was not included. It would be expected that patients who receive avelumab would have longer PFS and OS compared to patients who did not, or could not, receive avelumab. As such, the incremental benefit of EV+PEM would be different when compared to each of these subgroups.

6.17 For the patient reported outcomes, the EV-302 trial used the brief pain inventory – short form (BPI-SF) to measure time to pain progression (TTPP), and the European Organization for the Research and Treatment of Cancer Quality of Life Core 30 questionnaire (EORTC QLQ-C30) and the EuroQOL 5-dimensions, 5-level questionnaire (EQ-5D-5L) to measure quality of life.

6.18 EV+PEM did not significantly prolong TTPP (HR=0.916; 2-sided p-value=0.48). The median TTPP was numerically longer in the EV+PEM arm (14.2 months) than in the Plat+Gem arm (10.0 months), noting that this outcome was both subjective and measurement was unblinded.

6.19 Change from baseline results for the EORTC QLC-C30 global QoL, functional, and symptom scores showed no notable changes over time for any of the domain scores, inclusive of general quality of life, functioning, and symptom scores in either treatment arm. Individual domains remained stable throughout treatment based on mean score by cycle.

6.20 In the EQ-5D-5L questionnaire, most patients in both arms had little to no problems across all domains, reflecting relatively high quality of life at baseline. The mean baseline visual analogue scale (VAS) scores were 72.8 in the EV+PEM arm and 69.7 in the Plat+Gem arm. The mean baseline Health State Index Scores (utility scores) were 0.844 and 0.818, respectively. During the treatment period, both VAS and utility scores remained stable with little to no change from baseline throughout the study period.

6.21 The results of the quality-of-life questionnaires appear to be incongruent with the observation of a higher rate of drug discontinuations with EV+PEM due to treatment emergent adverse events (TEAEs). This was not explained in the submission.

Comparative harms

6.22 A summary of the safety results in the EV-302 trial is presented in Table 6. Analyses of safety were conducted in the safety analysis set (SAS) which consisted of all patients who received any study treatment.

Table 6: Summary of unadjusted key adverse events in the trials

AE category	EV+PEM N=440 n, (%)	Plat+Gem N=433 n, (%)	Risk Difference (95% CI) [a]	Risk Ratio (95% CI) [a]
Any TEAE	439 (99.8)	427 (98.6)	0.01 (-0.00, 0.02)	1.01 (0.10, 1.02)
Treatment related	427 (97.0)	414 (95.6)	0.01 (-0.01, 0.04)	1.01 (0.99, 1.04)
Grade 3-5 TEAE	321 (73.0)	341 (78.8)	**-0.06 (-0.12, -0.00)**	**0.93 (0.86, 0.99)**
Treatment related	246 (55.9)	301 (69.5)	**-0.14 (-0.20, -0.07)**	**080 (0.72, 0.89)**
Serious TEAE	220 (50.0)	169 (39.0)	**0.11 (0.04, 0.18)**	**1.28 (1.10. 1.49)**
Treatment related	122 (27.7)	85 (19.6)	**0.08 (0.02, 0.14)**	**1.41 (1.11, 1.80)**
TEAE leading to death	19 (4.3)	14 (3.2)	0.01 (-0.01, 0.04)	1.34 (0.68, 2.63)
Treatment related	4 (0.9)	4 (0.9)	-0.00 (-0.01, 0.01)	0.98 (0.25, 3.91)
TEAE leading to study drug discontinuation	175 (39.8)	93 (21.5)	**0.18 (0.12, 0.24)**	**1.85 (1.50, 2.29)**
Treatment related	154 (35.0)	80 (18.5)	**0.17 (0.11, 0.22)**	**1.89 (1.50, 2.40)**
TEAE leading to study drug interruption	347 (78.9)	279 (64.4)	**0.144 (0.09, 0.20)**	**1.22 (1.12, 1.33)**
Treatment related	299 (68.0)	229 (52.9)	**0.15 (0.09, 0.21)**	**1.28 (1.15, 1.43)**
TEAE leading to dose reduction	184 (41.8)	177 (40.9)	0.01 (-0.06, 0.07)	1.02 (0.87, 1.20)
Treatment related	179 (40.7)	164 (37.9)	0.03 (-0.04, 0.09)	1.07 (0.91, 1.27)

Source: Table 2-18, p77 of the submission.

AE = adverse event; EV+Pem = enfortumab vedotin with pembrolizumab; n = number of participants reporting data; N = total participants in group; Plat+Gem = platinum containing chemotherapy with gemcitabine; SAS safety analysis set; TEAEs = treatment emergent adverse events.

Bold = statistically significant

[a] calculated during the evaluation using Stata/MP 18.0.

6.23 The submission noted that EV+PEM was administered for a longer duration than Plat+Gem (median 9.43 months vs. median 4.14 months). Based on this, exposure adjusted adverse events were presented. However, the difference in exposure time was likely due to EV+PEM being administered until disease progression, whereas Plat+Gem is administered for a maximum of 6 cycles. As EV+PEM increases PFS, it is likely that the greater exposure seen in the EV-302 trial will be replicated in clinical practice. As such the unadjusted adverse events are more representative of what patients will experience and so are presented in the evaluation. The ESC agreed with the evaluation that use of the unadjusted adverse events was appropriate in considering the comparative harms.

6.24 Grade 3 to 5 TEAEs occurred at a higher rate in the Plat+Gem arm (78.8% vs. 73%). Similar proportions of patients were seen in both EV+PEM and Plat+Gem arms with any TEAE (99.8% vs. 98.6%, respectively), TEAE leading to death (4.3% vs. 3.2%, respectively), or TEAE leading to dose reduction (41.8% vs. 40.9%, respectively). However, the ESC noted that EV+PEM had a higher rate of TEAEs leading to study drug interruption (78.9% vs. 64.4%), and a higher rate of serious TEAEs (50.0% *vs*. 39.0%) compared to Plat+Gem. In addition, EV+PEM had nearly double the rate of TEAEs leading to discontinuation (39.8% vs. 21.5%). The most common TEAE leading to discontinuation of EV was peripheral sensory neuropathy (11.1%) with pneumonitis (2.0%) the most common TEAE leading to discontinuation of PEM. In the Plat+Gem arm the most common TEAE leading to discontinuation was anaemia (2.8%).

Table 7: NCI CTCAE Grade 3 or higher TEAE, with frequency ≥ 2% in either treatment arm (SAS)

Preferred Term	EV+PEM N=440		Plat+Gem N=433	
	All cause n (%)	Treatment-related n (%)	All cause n (%)	Treatment-related n (%)
Overall	321 (73.0)	246 (55.9)	341 (78.8)	301 (69.5)
Rash maculo-papular	36 (8.2)	34 (7.7)	0	0
Hyperglycaemia	32 (7.3)	22 (5.0)	3 (0.7)	0
Anaemia	31 (7.0)	15 (3.4)	148 (34.2)	136 (31.4)
Acute kidney injury	22 (5.0)	10 (2.3)	10 (2.3)	7 (1.6)
Hyponatraemia	22 (5.0)	12 (2.7)	15 (3.5)	8 (1.8)
Neutropenia	22 (5.0)	21 (4.8)	130 (30.0)	130 (30.0)
Urinary tract infection	22 (5.0)	3 (0.7)	35 (8.1)	4 (0.9)
Diarrhoea	21 (4.8)	16 (3.6)	6 (1.4)	3 (0.7)
Fatigue	17 (3.9)	13 (3.0)	20 (4.6)	18 (4.2)
Peripheral sensory neuropathy	17 (3.9)	16 (3.6)	0	0
Weight decreased	16 (3.6)	8 (1.8)	1 (0.2)	1 (0.2)
Pulmonary embolism	14 (3.2)	0	17 (3.9)	7 (1.6)
Neutrophil count decreased	11 (2.5)	11 (2.5)	40 (9.2)	39 (9.0)
Asthenia	10 (2.3)	8 (1.8)	11 (2.5)	10 (2.3)
Pneumonia	10 (2.3)	1 (0.2)	4 (0.9)	1 (0.2)
Alanine aminotransferase increased	9 (2.0)	9 (2.0)	3 (0.7)	3 (0.7)
Hypophosphataemia	9 (2.0)	4 (0.9)	5 (1.2)	4 (0.9)
Lipase increased	9 (2.0)	8 (1.8)	0	0
Haematuria	7 (1.6)	0	10 (2.3)	4 (0.9)
Nausea	7 (1.6)	5 (1.1)	12 (2.8)	12 (2.8)
Febrile neutropenia	4 (0.9)	4 (0.9)	14 (3.2)	13 (3.0)
Leukopenia	4 (0.9)	3 (0.7)	20 (4.6)	19 (4.4)
Thrombocytopenia	4 (0.9)	2 (0.5)	87 (20.1)	84 (19.4)
White blood cell count decreased	1 (0.2)	1 (0.2)	13 (3.0)	13 (3.0)
Platelet count decreased	0	0	29 (6.7)	28 (6.5)

Source: Table 2-19, p78 of the submission.

EV+Pem = enfortumab vedotin with pembrolizumab; n = number of participants reporting data; N = total participants in group; NCI CTCAE = National Cancer Institute common terminology criteria for adverse events; Plat+Gem = platinum containing chemotherapy with gemcitabine; SAS = safety analysis set; TEAE = treatment-emergent adverse event.

6.25 Table 7 displays the frequency of Grade ≥3 TEAEs. These data show that each treatment has a different safety profile. The Plat+Gem arm had 3 AEs that were widely reported, anaemia (34.2%), neutropenia (30%), and thrombocytopenia (20.1%). This contrasts with the EV+PEM arm where no singular AE was reported in more than 10% of patients, but a broader range were reported more commonly than in Plat+Gem, the most common of which were maculo-papular rash (8.2%), hyperglycaemia (7.3%), and anaemia (7.0%). The ESC considered the types of Grade ≥3 AEs experienced by patients receiving EV+PEM were more likely to impact on a patient's quality of life

(e.g., rash, peripheral neuropathy) and those experienced by patients receiving Plat+Gem were likely to be transient and manageable (e.g., anaemia, neutropenia).

Benefits/harms

6.26 A summary of the comparative benefits and harms for EV+PEM versus Plat+Gem is presented in Table 8.

Table 8: Summary of comparative benefits and harms for EV+PEM versus Plat+Gem

Progression free survival by BICR (median duration of follow up 17.2 months)				
Event	**EV+PEM**	**Plat+Gem**	**Absolute Difference**	**HR (95% CI)**
Progressed, n (%)	223/442 (50.5%)	307/444 (69.1%)	-	**0.45 (0.38, 0.54)**
Median PFS, months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)	6.2	
PFS rate (%) at 6 months (95% CI)	72.8 (68.3, 76.8)	60.7 (55.7, 65.4)	12.1% [a]	
PFS rate (%) at 12 months (95% CI)	50.7 (45.6, 55.5)	21.6 (17.2, 26.2)	29.1% [a]	
PFS rate (%) at 18 months (95% CI)	43.9 (38.5, 49.1)	11.7 (8.0, 16.1)	32.3% [a]	
Overall survival (median duration of follow up 17.2 months)				
Deaths, n/N (%)	133/422 (30.1%)	226/444 (50.9%)	-	**0.47 (0.38, 0.58)**
Median OS, months (95% CI)	31.5 (25.4, NR)	16.1 (13.9, 18.3)	15.4	
OS rate (%) at 6 months (95% CI)	90.2 (87.0, 92.6)	81.9 (77.9, 85.2)	8.3% [a]	
OS rate (%) at 12 months (95% CI)	78.2 (73.9, 81.9)	61.4 (56.6, 65.9)	16.8% [a]	
OS rate (%) at 18 months (95% CI)	69.5 (64.4, 74.1)	44.7 (39.2, 50.1)	24.8% [a]	

Harms						
	EV+PEM n/N	**Plat+Gem n/N**	**RR (95% CI) [a]**	**Event rate/100 patients**		**RD (95% CI) [a]**
				EV+PEM	**Plat+Gem**	
Grade 3-5 TEAE	321/440	341/433	**0.93 (0.86, 1.0)**	73	79	**-0.06 (-0.12, -0.00)**
TEAE leading to discontinuation	175/440	93/433	**1.85 (1.49, 2.29)**	40	22	**0.18 (0.12, 0.24)**
TEAE leading to dose interruption	347/440	279/433	**1.22 (1.12, 1.33)**	79	64	**0.14 (0.09, 0.20)**

Source: Table 2-12, p66, Table 2-13, p68, and Table 2-18, p77 of the submission.
BICR = blinded independent central review; CI = confidence interval; EV+PEM = enfortumab vedotin with pembrolizumab; HR = hazard ratio; ITT = intention to treat population; OS = overall survival; PFS = progression free survival; Plat+GEM = platinum containing chemotherapy with gemcitabine; n = number of patients who progressed or died; N = number of patients in the arm; NR = not reached; RD = risk difference; RR = risk ratio; TEAE = treatment emergent adverse event.
Bold = statistically significant
[a] calculated using Stat/MP 18.0

6.27 On the basis of direct evidence presented by the submission, for every 100 patients treated with EV+PEM in comparison with Plat+Gem over a median duration of follow-up of 17.2 months:

- Approximately 29 fewer patients would have disease progression at 12 months.
- Approximately 17 fewer patients would have died at 12 months.
- Approximately 6 fewer patients would experience a grade 3-5 adverse event
- Approximately 18 additional patients would experience an adverse event requiring drug discontinuation.

- Approximately 14 additional patients would experience an adverse event requiring a dose interruption.

Clinical claim

6.28 The submission described EV+PEM as superior in terms of effectiveness and safety compared with Plat+Gem in patients with previously untreated la/mUC.

6.29 The evaluation considered that the therapeutic conclusion of superior efficacy is adequately supported by the clinical evidence presented. EV+PEM demonstrated a statistically significant improvement in PFS by BICR in the ITT population compared to Plat+Gem (HR=0.45; 95% CI: 0.38, 0.54) with an incremental gain in median PFS of 6.2 months. A statistically significant improvement in OS with EV+PEM was also observed (HR=0.468; 95% CI: 0.376, 0.582) with an incremental gain in median OS of 15.4 months. The ESC agreed with the evaluation that the claim of superior efficacy is supported by the evidence presented. However, the ESC considered the magnitude of benefit may potentially be overestimated due to the absence of a subgroup analysis to show the incremental benefit of EV+PEM over Plat+Gem by the presence or absence of avelumab maintenance therapy.

6.30 The evaluation considered the therapeutic conclusion of superior safety is not adequately supported by the clinical evidence presented. The submission made the claim of superior safety based on exposure adjusted adverse events rates as EV+PEM was administered for a longer duration than Plat+Gem (median 9.43 months vs. median 4.14 months). However, the difference in exposure time was likely due to EV+PEM being administered until disease progression, whereas Plat+Gem is administered for a maximum of 6 cycles. As EV+PEM increases PFS, it would be expected that the greater exposure seen in the EV-302 trial will be mirrored in clinical practice. As such, the unadjusted adverse event rates are more representative of what patients will experience. When looking at the unadjusted TEAEs rates, Plat+Gem had a higher rate of grade 3 to 5 TEAEs (78.8% vs. 73%). However, EV+PEM had a higher rate of TEAEs leading to discontinuation (39.8% vs. 21.5%), a higher rate of TEAEs leading to study drug interruption (78.9% vs. 64.4%) and a higher rate of serious TEAEs (50.0% *vs*. 39.0%). Due to the differences in mechanism of action and administration and adverse event profiles, the evaluation considered a claim of non-inferior but different safety is more reasonable. The PSCR acknowledged that superior safety is difficult to establish based on a direct comparison of the safety data between treatment arms and agreed with the evaluation that a claim of non-inferior but different safety is reasonable. The ESC agreed with the evaluation that the unadjusted adverse event rates should be used but advised that a claim of inferior but manageable safety profile may be more appropriate.

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

6.32 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data. Instead the PBAC agreed with the ESC that a claim of inferior but manageable safety profile was appropriate.

Economic analysis

6.33 The submission presented a modelled economic evaluation of EV+PEM compared with Plat+Gem for the treatment of patients with la/mUC. Comparative effectiveness, safety and time on treatment data were derived from the key randomised trial – EV-302. Consistent with the claim of superior effectiveness and superior safety, the economic evaluation was a cost-effectiveness / cost-utility analysis.

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

Component	Description	Justification/comments
Treatments	Enfortumab vedotin + Pembrolizumab vs Platinum chemotherapy + Gemcitabine	Australian clinical practice involves the use of avelumab in the maintenance setting (post-platinum therapy). The model inputs were derived from EV-302 with some use of avelumab captured in this trial (see paragraph 6.8). This was reasonable.
Outcomes	Life-years gained and quality-adjusted life-years gained	These outcomes were reasonable.
Time horizon	15 years in the model base case vs 17.2 months of median follow up.	The modelled OS extrapolation for EV+PEM predicts that approximately 8.5% of patients will remain alive at 10 years. The evaluation noted a time horizon of 15 years is likely necessary to completely capture patient survival. However, the evaluation considered that incorporating background mortality and an older cohort in the model would result in a time horizon of 10 years being adequate. PBAC has previously considered that a 7.5 year time horizon would be appropriate for capturing the effects of treatments for locally advanced or metastatic urothelial cancer (paragraph 7.10, 6.02 Avelumab, public summary document, March 2021 PBAC meeting).
Methods used to generate results	Partitioned survival analysis (with separate time on treatment curves)	This approach was reasonable.
Health states	Progression-free, progressed and dead	The health states were reasonable.
Cycle length	1 week	This was reasonable.

Component	Description	Justification/comments
Transition probabilities	Health state allocation is determined by the PFS curve and OS curve from EV-302, initially using the Kaplan-Meier data, then using a parametric extrapolation. On-treatment and off-treatment status is estimated separately. For EV+PEM and Plat+GEM, time on treatment curves were used to estimate the proportion of patients remaining on treatment. For subsequent therapies, time on treatment is derived from IPD analysis of EV-302 except for subsequent use of EV, which is derived from EV-301. Costs are front-loaded upon progression.	For estimating the duration of treatment of index treatments, this approach was reasonable. The duration of subsequent treatments was reasonable except for the duration of subsequent line EV, which was derived from EV-301 and likely overestimates the duration of treatment.
Extrapolation method	PFS, OS and time on treatment curves were extrapolated using independently fit parametric functions. Parametric functions are used after median follow up (17.2 months).	The method of extrapolation was reasonable. Kaplan-Meier curves were reliable beyond median follow-up. Observed data could have been used for a greater duration.
Health-related quality of life	Utilities for the progression-free and progressed health states were estimated from EQ-5D-5L data collected during EV-302.	Compliance in completing EQ-5D-5L questionnaires was commonly below 80%. Estimates of utility may have been affected by nonresponse. The model is sensitive to the nominated utilities. The nominated utilities for a previous submission considered by PBAC were lower (Table 12, 6.02 Avelumab PSD, March 2021 PBAC meeting).
Perspective	Australian health care system, including only direct health-related costs and health-related outcomes.	This was reasonable.
Discounting	5% per annum (applied weekly).	This was reasonable.

Source: adapted from Table 3-1, p89 of the submission.
EQ-5D-5L = EuroQOL 5-dimensions; EV = Enfortumab vedotin; Gem = Gemcitabine; PBAC = Pharmaceutical Benefits Advisory Committee; PEM = Pembrolizumab; PSD = Public summary document; Plat = Platinum-based chemotherapy; RCT = Randomised, controlled trial; SOC = System Organ Class

6.34 The submission nominated a 15-year time horizon. This is considerably longer than the time horizon recommended by ESC and PBAC (7.5 years) in its consideration of avelumab for use as maintenance therapy following treatment with platinum chemotherapy for la/mUC. Although the proportion of patients remaining alive in the comparator arm at 7.5 years was low (6.35% in the base case), most plausible extrapolations for the EV+PEM arm indicated survival for at least 10% of patients. The PSCR noted that in the base case economic analysis, at 10 years 8.47% of EV+PEM patients were expected to remain alive, compared to 4.08% of Plat+Gem patients. The ESC noted accounting for background mortality resulted in 7.20% of EV+PEM and 0.35% of Plat+Gem patients being alive at 10 years. The pre-PBAC response accepted a reduction in the time horizon in the model from 15 years to 10 years.

6.35 The population included in the economic evaluation was the same as was included in EV-302. The population included in the model (67.9 years) was younger than the

average age of patients with bladder cancer in Australia (75.3 years[16]). Although the age in the model could be adjusted, the model provided with the submission did not use a reasonable method to account for background mortality, and adjusting the age had no impact on OS. During the evaluation, background mortality was applied to the parametric extrapolation of OS curves in both arms, and the age in the model was increased. As the mortality associated with la/mUC is high, the adjustments made during the evaluation had only a small impact. The impact of incorporating background mortality associated with an average age of 75.3 years is presented in Figure 4. The ESC noted that while the average age of PBS-eligible patients may be higher than the trial population, it may not be as high as the average age of bladder cancer patients in Australia, which would include older patients not eligible for treatment. The ESC considered an assumption of an average age of 72 years would be reasonable to inform background mortality estimate. The pre-PBAC response agreed with the modifications to the model to incorporate background mortality and with updating the average age to 72 years.

6.36 It is unlikely that the adjustment made during the evaluation adequately captures the increased mortality associated with a diagnosis of urothelial cancer at an older age. Kaplan-Meier curves by age groups were not available in the submission or the EV-302 clinical study report (CSR), but were provided by the sponsor during the evaluation. Although survival in the older age group (≥65 years) was lower than survival in the total EV-302 population (included in the model), the absolute benefit of EV+PEM appeared to be maintained.

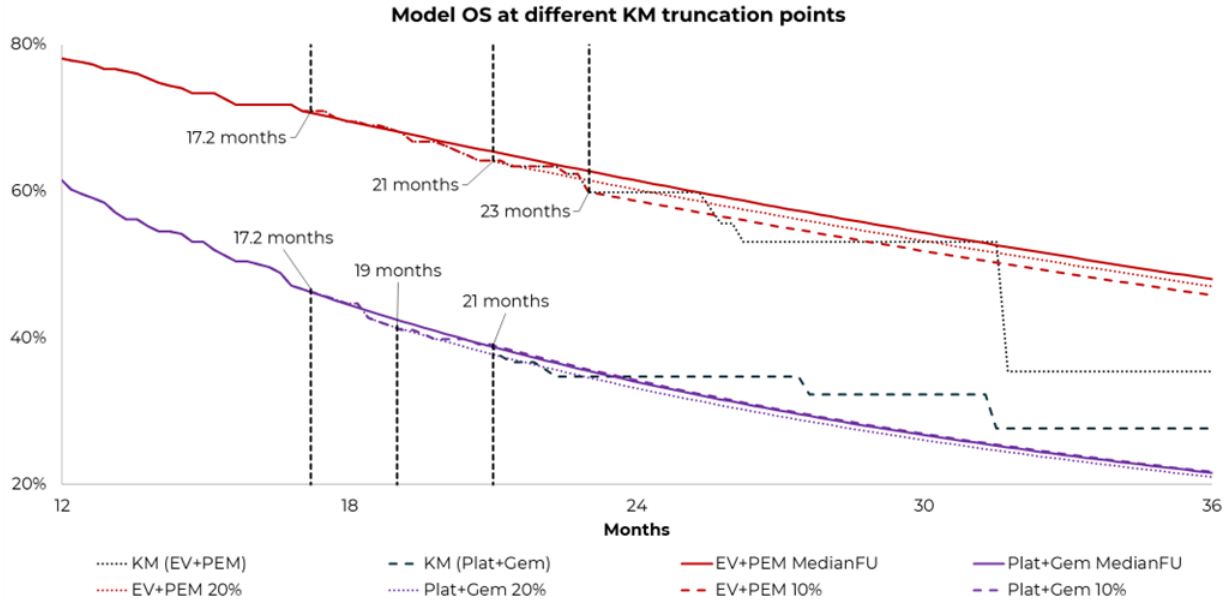
6.37 The extent of use of maintenance avelumab in the model reflected the use of maintenance PD-(L)1 therapies in the key trial. It is unclear whether the use of maintenance PD-(L)1 therapies was lower in EV-302 (32%) compared with the Australian setting. If it was lower, this may have both cost and effectiveness implications for the model. However, as the use of other subsequent PD-(L)1 therapies was close to 30% (and only 70% of patients had a recorded progression event), then exposure to PD-(L)1 therapies in the Plat+Gem arm of EV-302 is reasonably high and therefore the OS curve in EV-302, applied in the model, is consistent with the use of PD-(L)1 therapies in Australia i.e. whether used as maintenance therapy or as subsequent therapy.

6.38 The economic evaluation applied observed (Kaplan-Meier) data until 17.2 months (median follow up in EV-302) in the base case and applied independently fit parametric functions extrapolated to the lifetime of the model. At median follow up, the Kaplan-Meier curves for OS indicated that there were more than 200 patients remaining at risk. There is no indication that the curves had become unstable. Applying a parametric function to extrapolate from median follow up leads to the EV+PEM extrapolated curve remaining above the remainder of the Kaplan-Meier

[16] Australian Institute of Health and Welfare (AIHW). Cancer Data in Australia. Canberra: AIHW.; 2023.

curve (Figure 3). The use of Kaplan-Meier data until there are 10% of patients remaining at risk may be more reasonable given the relative stability of the Kaplan-Meier curve, and the large number of patients in the trial. Varying the truncation point for the PFS extrapolation does not have an impact on the model (as PFS is more complete at 17.2 months). The ESC noted the approach outlined in Gebski et al (2018)[17] would provide a methodologically robust method for estimating an appropriate KM truncation point. Using a truncation point of 26 months for OS for EV+PEM and 28 months for Plat+Gem increased the ICER by 15.1%. The pre-PBAC response accepted the use of the approach outlined in Gebski et al (2018) as proposed by the ESC.

Figure 3: Visual comparison of using alternative truncation points for extrapolation for EV+PEM and Plat+Gem



Source: generated during the evaluation from the economic evaluation excel spreadsheet.
Note: x-axis is trimmed to show detail of the impact of nominating an alternative truncation point for the use of Kaplan-Meier data. The vertical lines on the graph represent the different truncation points based on median follow up in the trial (17.2 months), or 20% remaining at risk (21 months for EV+PEM and 19 months for Plat+Gem), or 10% remaining at risk (23 moths for EV+PEM and 21 months for Plat+Gem).

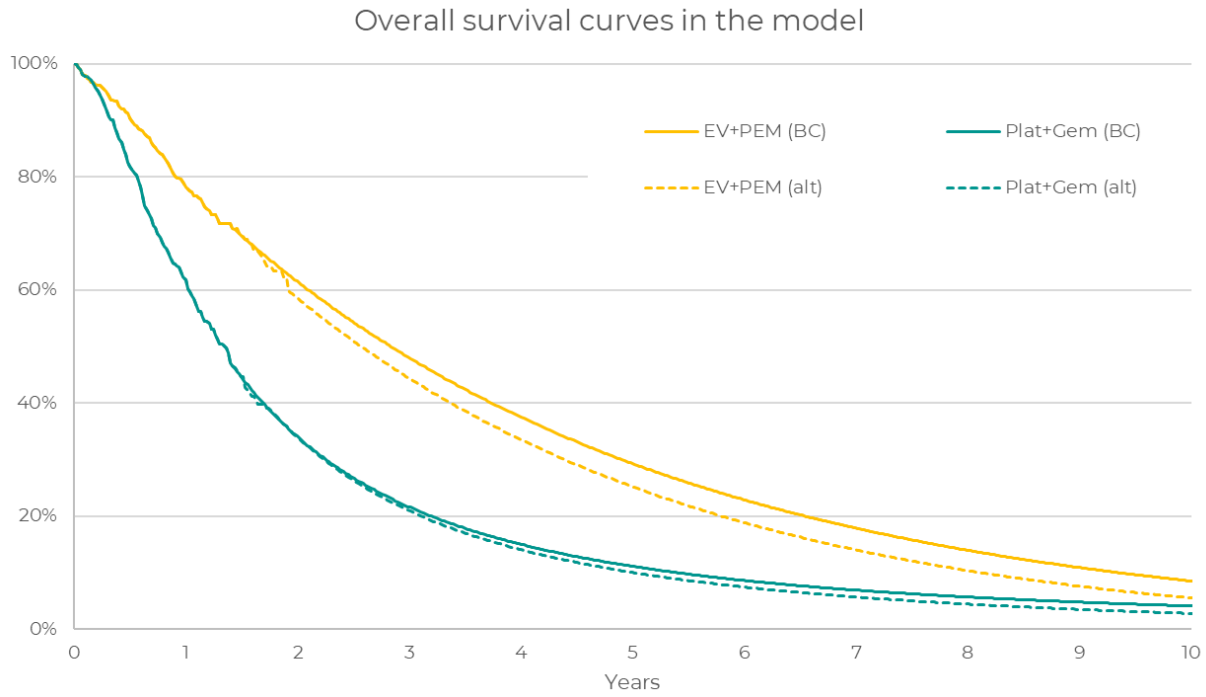
6.39 The submission nominated different parametric functions for extrapolating OS for each of the model arms. The submission justified the use of independent parametric functions on the basis that the two model arms had treatments with differing mechanisms of action. As such, dependent curves were not presented. It is unclear whether this approach was adequately justified. The nominated extrapolation function for the Plat+Gem arm was the log-logistic function. This was reasonable and was supported by OS in observational data.

[17] Gebski, V., Garès, V., Gibbs, E., & Byth, K. (2018). Data maturity and follow-up in time-to-event analyses. International Journal of Epidemiology, 47(3), 850–859.

6.40 The submission nominated the exponential curve to extrapolate OS in the EV+PEM arm. There was no clear statistical difference between most of the possible parametric functions, and the submission did not provide a discussion of the clinical plausibility of the nominated function. The exponential function results in a 10 year survival that is 8.47% (compared with 4.08% in the Plat+Gem arm). Alternative functions predict lower survival or implausibly higher survival. Assuming that the PFS curves were reasonable (PFS is more mature than OS), the exponential curve results in a similar duration of post-progression survival compared with the Plat+Gem arm. The exponential function appears to be a reasonable fit.

6.41 Modelled OS in the submission's base case, after incorporating background mortality and increasing the age in the model, is presented in Figure 4, below.

Figure 4: Base case overall survival curves and with alternative base case (incorporating background mortality, increased age and change in proposed truncation point for the use of Kaplan-Meier data)



Source: generated during the evaluation from the economic evaluation excel spreadsheet.
BC = submission base case: 67.9 years of age, no addition of background mortality into the parametric extrapolations, exponential extrapolation for EV+PEM, log-logistic extrapolation for Plat+Gem, use of Kaplan-Meier data until median follow up (17.2 months)
Alt = incorporation of higher age (75.3 years), addition of background mortality into the parametric extrapolations, the same extrapolations used as per the submission base case, and the use of Kaplan-Meier data until 10% remaining at risk.

6.42 The submission applied a log-normal and log-logistic parametric function to the PFS Kaplan-Meier curves of the EV+PEM arm and Plat+Gem arm, respectively, after 17.2 months (median follow up in the EV-302 trial). The model was not sensitive to the choice of parametric function, or to the duration of use of Kaplan-Meier data before changing to a parametric function. It is reasonable that the nominated parametric function was different across the arms, as the mechanism of action differs for EV+PEM and Plat+Gem.

6.43 Time on treatment was sourced from EV-302. The time on treatment curve for Plat+Gem was mature, and no extrapolation was required. The time on treatment curve for maintenance avelumab was extrapolated from 17.2 months using a Weibull function. It is likely that the Weibull function overestimates the duration of avelumab treatment, as it predicts an average duration of treatment of 16.5 months. However, the treatment duration in the economic model is capped by the Plat+Gem PFS curve, which results in an average treatment duration of 12.98 months. In its consideration of avelumab maintenance treatment for urothelial cancer, the PBAC considered the exponential function best represented time on treatment, and this extrapolation predicted an average treatment duration of 12.64 months (paragraph 4.6, 4.02 Avelumab Public Summary Document, March 2022 PBAC meeting).

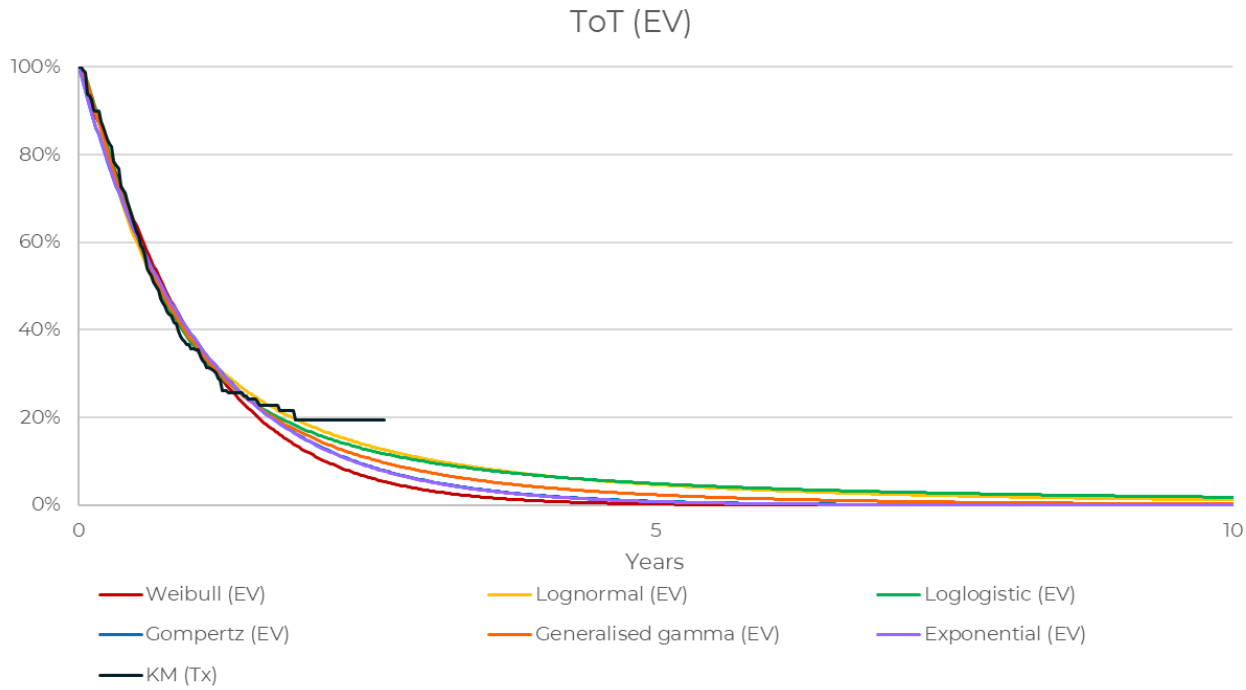
6.44 Time on treatment for EV was extrapolated beyond 17.2 months of Kaplan-Meier data using the generalised gamma function. Statistically, the best fitting extrapolation was the log-logistic curve, however this resulted in an average treatment duration that was considered to be implausible by the submission. The choice of extrapolation was poorly justified. The model was moderately sensitive to the choice of extrapolation for duration of EV treatment. The ESC noted that, in addition to being the best statistical fit, the log-logistic extrapolation appeared to fit the data reasonably well (Figure 5). The pre-PBAC response maintained that the generalised gamma function was the more reasonable and clinically relevant choice for EV. The pre-PBAC response noted using a log-logistic extrapolation resulted in a treatment duration that was less clinically plausible and inconsistent with the observed data from EV-302 where the mean ToT was shorter for EV than for PEM. The PBAC noted the mean ToT in the EV-302 study was a truncated mean and more patients remained on EV than PEM at data cutoff.

Table 10: Impact of alternative parametric functions fitted to the EV time on treatment Kaplan-Meier data

	Mean treatment duration (months)	ICER	ICER, Change from base case
Exponential	12.5	[redacted][1]	-[redacted]%
Weibull	11.9	[redacted][1]	-[redacted]%
Log-normal	15.5	[redacted][1]	[redacted]%
Log-logistic	15.9	[redacted][1]	[redacted]%
Gompertz	12.6	[redacted][1]	-[redacted]%
Generalised gamma	13.8	[redacted][1]	Base case

Source: generated during the evaluation from the economic evaluation spreadsheet.
EV = Enfortumab vedotin; ICER = Incremental cost-effectiveness ratio
The redacted values correspond to the following ranges:
1 $155,000 to < $255,000

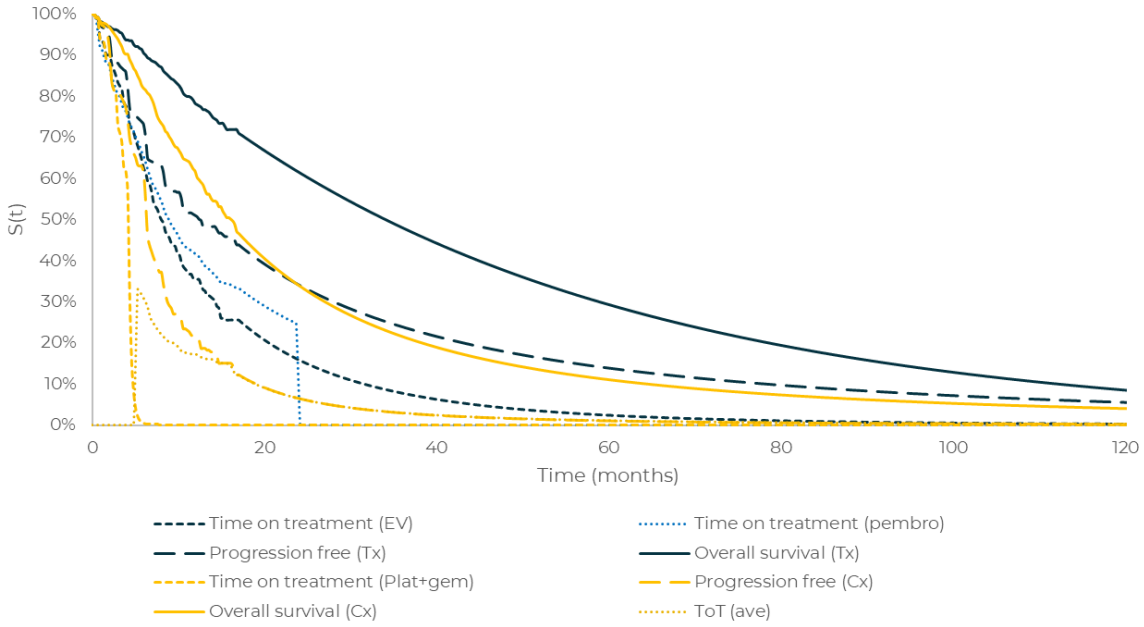
Figure 5: Time to treatment discontinuation curves for enfortumab vedotin in the EV+PEM arm



Source: Figure 3-7, p99 of the submission.
EV = enfortumab vedotin; KM = Kaplan-Meier; PEM = pembrolizumab; ToT = time on treatment; Tx = treatment arm in EV-302 containing enfortumab vedotin and pembrolizumab – in this figure, only the KM curve for enfortumab vedotin is presented.

6.45 The time on treatment curve for PEM was reasonably mature, and the model assumed that patients remaining on treatment would cease at 2 years. This assumption was consistent with PBS listings for PEM that include a maximum treatment duration with PD-(L)1 inhibitors of 2 years. The model (and the treatment duration of PEM) was not sensitive to the choice of extrapolation for PEM time on treatment.

Figure 6: Kaplan-Meier data and extrapolation graphs for the modelled economic evaluation



Source: Figure 3-12, p109 of the submission.
Ave = avelumab; Cx = Plat+Gem arm; EV = enfortumab vedotin; gem = gemcitabine; pembro = pembrolizumab; Plat = platinum chemotherapy; S(t) = proportion surviving; Tx = enfortumab vedotin + pembrolizumab arm.

6.46 The submission sourced quality-of-life estimates from EQ-5D-5L questionnaires administered in EV-302. Utilities were derived using Australian-specific value sets[18]. The submission noted that utilities were available from the assessment of avelumab used in the maintenance setting, however dismissed these as not appropriate as they are based on a different treatment and population. This claim is not well supported. The utilities used in the avelumab submission have been considered by PBAC (Table 12, 6.02 avelumab, PSD, March 2021 PBAC meeting). The base case ICER increased by 7.4% when the utilities from the Avelumab PSD were used. The PSCR argued that in order to ensure internal validity of the model, trial-based utilities derived from Australian tariffs were used in the base case economic evaluation.

6.47 The submission included index drug costs, drug costs for subsequent lines of treatment, administration costs, costs associated with Grade 3+ adverse events, costs associated with disease management in each health state, and terminal care costs.

6.48 Published drug costs were used for platinum chemotherapies, gemcitabine and pre-medications. The submission applied a 50% discount to the published prices for avelumab and PEM (when used in the 2L setting) as these drugs have special pricing arrangements. The effective price of EV was applied when used in the later line.

[18] Norman R, Mulhern B, Lancsar E, Lorgelly P, Ratcliffe J, Street D, Viney R. The Use of a Discrete Choice Experiment Including Both Duration and Dead for the Development of an EQ-5D-5L Value Set for Australia. Pharmacoeconomics. 2023;41(4):427-38.

6.49 The submission has used the proposed published prices for EV and PEM when used in the 1L setting. However, the submission has back calculated the total cost of combined EV and PEM in order to achieve an ICER of $75,000 to < $95,000/QALY.

6.50 The submission estimated the cost of subsequent treatments based on the proportion of patients in EV-302 that received subsequent treatments. This was not reasonable. Only 50% of patients receiving EV+PEM and 70% of patients receiving Plat+Gem were recorded as progressed in EV-302. As all patients will eventually progress, a greater proportion will receive subsequent treatments than was recorded in EV-302. Adjusting for the number who have progressed in the Plat+Gem arm, all patients would, on average, receive an additional line of treatment. As the post-progression period was estimated to be similar across the arms, it may be reasonable to assume that all patients across both arms will receive, on average, one additional line of therapy. This assumption increases the use of post-progression therapies in the EV+PEM arm to a greater extent than the Plat+Gem arm, however, as therapies available to the patients progressing on Plat+Gem are more costly, the overall cost in the Plat+Gem arm increases more.

6.51 The duration of treatment with post-progression PEM and chemotherapy was informed by an individual patient data (IPD) analysis of EV-302. This is reasonable. However, the duration of treatment with post-progression EV was informed by the average duration of treatment in the EV-301 study. This is not appropriate. Patients enrolled in EV-301 met eligibility criteria and were likely to be fitter than the average patient receiving later line treatment with EV in EV-302. The base case analysis was not sensitive to the duration of treatment of later-line EV.

6.52 Terminal care costs were derived from a study of the direct healthcare costs of different cancer types incurred over the final year of life. The study separated out MBS and PBS costs from the overall cost and the submission removed these to avoid double counting. The resulting cost was then inflated to 2023 Australian dollars using the Reserve Bank of Australia (RBA) inflation calculator. The cost of terminal care, estimated to be $45,000 to < $55,000, is applied in the model on transition to death. As fewer patients in the EV+PEM arm transition to death within the time horizon, this cost is applied in a higher proportion of patients in the Plat+Gem arm. The evaluation considered this was inappropriate as there is no indication that EV+PEM results in a cure, all patients will die with or of la/mUC and will incur costs associated with terminal care. The ESC noted removal of terminal care costs increased the ICER by <2% for the base case model provided in the submission and the respecified ESC base case model. The pre-PBAC response argued that terminal care costs should be retained in the model as, although not a cure, the survival benefits afforded by EV+PEM will result in terminal care costs being incurred at a later time compared to Plat+Gem, and these will be discounted. The PBAC noted there were 6% of patients alive in the EV arm at 10 years compared to 3% in the Plat+Gem arm in the respecified economic model.

6.53 The key drivers of the model are presented in Table 11. The impact on the ICER should be interpreted in the context of the submission base case ICER, which is

$155,000 to < $255,000. Therefore, even small percentage changes to the ICER may reflect large absolute changes in costs or outcomes.

Table 11: Key drivers of the model

Description	Method/Value	Impact Base case: [redacted][1]/QALY gained
Overall survival	The average age of bladder cancer patients in the Australian setting is 75.3 years. The average age of patients in EV-302 was 67.9 years. • Background mortality was not appropriately accounted for in the model. • Subgroup analysis of patients <65 years vs ≥65 years indicated that survival is considerably longer for the younger age group. The relative benefit of EV+PEM appeared stable across the age groups presented in EV-302. However, the absolute benefit of EV+PEM vs Plat+Gem was lower in older age groups.	High, favours EV+PEM Incorporating background mortality and increasing the age in the model increases the ICER by 9.6%. The impact of the use of more favourable survival curves derived from EV-302 cannot be measured but will favour EV+PEM.
Truncation point	The submission used Kaplan-Meier data to 17.2 months (median follow up in the EV-302 study). Given the size of the study, the apparent stability of the Kaplan-Meier curve, and the projection of the parametric functions at different truncation points, it was reasonable to use Kaplan-Meier data until only 10% of patients remained at risk.	Moderate, favours EV+PEM Using the later truncation point results in an increase in the ICER of 6.8%.
Utilities	The utility values for the model health states were derived from EQ-5D-5L data from EV-302. Questionnaire compliance was low in EV-302, and no discussion was provided regarding the nature of the nonresponse. The utility values from the avelumab submission (Table 12, 6.02 Avelumab PSD, March 2021 PBAC meeting).	Moderate, favours EV+PEM Using the lower utility values results in an increase in the ICER by 7.4%.

Source: generated during the evaluation from the economic model spreadsheet.
EQ-5D-5L = EuroQOL 5-dimensions; EV = Enfortumab vedotin; Gem = Gemcitabine; ICER = Incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; PEM = Pembrolizumab; PSD = Public summary document; Plat = Platinum-based chemotherapy; QALY = Quality-adjusted life-year
The redacted values correspond to the following ranges:
1 $155,000 to < $255,000

6.54 The submission base case resulted in an ICER of $155,000 to < $255,000 per additional QALY. The stepped analysis presented in the submission includes a modelled analysis truncated at three years that reported cost per additional LY, the same analysis extended to 15 years, and a modelled analysis at 15 years that reported cost per additional QALY (Table 12).

Table 12: Results of the stepped analysis (submission base case) using published EV + PEM prices

Step	Cost ($)	Incremental cost ($)	Effectiveness	Incremental effectiveness	ICER
Step 1: Cost per LY over 3-year trial horizon					
EV+PEM	[redacted]		2.013	0.545	[redacted][1]
Plat+Gem			1.468		
Step 2: Cost per LY over a 15-year time horizon					
EV+PEM	[redacted]		3.372	1.329	[redacted][2]
Plat+Gem			2.043		
Step 3: Cost per QALY over a 15-year time horizon					
EV+PEM	[redacted]	$[redacted]	2.704	1.104	[redacted][2]
Plat+Gem			1.599		

Source: Table 3-22, p111 of the submission.
EV = Enfortumab vedotin; Gem = Gemcitabine; ICER = Incremental cost-effectiveness ratio; LY = Life year; PEM = Pembrolizumab; Plat = Platinum-based chemotherapy; QALY = Quality-adjusted life-year
The redacted values correspond to the following ranges:
1 $355,000 to < $455,000
2 $155,000 to < $255,000

6.55 These results were based on the proposed published price of EV and PEM, and on prices for avelumab and PEM (2L) that were 50% of the published price. The base case ICER $155,000 to < $255,000) is derived using a combined treatment cost of EV+PEM of $[redacted] (discounted; $[redacted] undiscounted) per patient. The submission has presented the combined price of EV+PEM required to achieve an ICER of $75,000 to < $95,000/QALY.

Table 13: Sensitivity analyses presented in the evaluation

SA#	Variable or assumption	ICER derived using published EV + PEM prices		Treatment cost required to achieve an ICER of $[redacted][1]/QALY	
		ICER	% Δ from Base Case	Estimated EV+PEM treatment cost (discounted) ($)	% Δ from Base Case
Base case		[redacted][2]	0.0%	[redacted]	0.0%
Mortality: base case = no background mortality applied to curves, average age 67.9 years					
1	Incorporate background mortality	[redacted][2]	[redacted]%	[redacted]	-[redacted]%
2	Increase age in model to 75.3 years	[redacted][2]	[redacted]%		[redacted]%
2a	Increase age in model to 72 years [a]	[redacted][2]	[redacted]%		[redacted]%
Use of KM data: base case 17.2 months for OS and PFS					
3	Use KM data until 10% remaining at risk (EV+PEM = 23 months; Plat+Gem = 21 months)	[redacted][2]	[redacted]%	[redacted]	-[redacted]%
3a	Use OS KM data up to Gebski et al 2018 criteria 2 (EV+PEM = 26 months; Plat+Gem = 28 months) [a]	[redacted][2]	[redacted]%		-[redacted]%
3b	Use PFS KM data up to Gebski et al 2018 criteria 2 (EV+PEM = 24 months; Plat+Gem = 24 months) [a]	[redacted][2]	[redacted]%		[redacted]%
Model time horizon: base case = 15 years					
4	Time horizon = 10 years	[redacted][2]	[redacted]%	[redacted]	-[redacted]%
4a	Time horizon = 7.5 years [a]	[redacted][2]	[redacted]%		-[redacted]%
Terminal care costs: base case = $52,291.45 upon transition to death					
5	Remove all terminal care costs	[redacted][2]	[redacted]%	[redacted]	-[redacted]%

SA#	Variable or assumption	ICER derived using published EV + PEM prices		Treatment cost required to achieve an ICER of $[redacted]1/QALY	
		ICER	% Δ from Base Case	Estimated EV+PEM treatment cost (discounted) ($)	% Δ from Base Case
Time on treatment extrapolation: base case = generalised gamma for EV and Weibull curve for avelumab					
6	Loglogistic curve for EV ToT (best fitting) [a]	[redacted]2	[redacted]%	[redacted]	-[redacted]%
Utility values: base case PF = 0.829, PD = 0.759 (from EV-302)					
7	PF = 0.772, PD = 0.698 (considered by PBAC for maintenance avelumab submission)	[redacted]2	[redacted]%	[redacted]	-[redacted]%
Treatment duration of maintenance avelumab: base case = Weibull extrapolation fitted to EV-302 data					
8	Exponential function fitted to EV-302 data	$[redacted]2	[redacted]%	[redacted]	-[redacted]%
MBS costs: base case includes prices that have been updated					
9	Updated prices (1/7/2024)	[redacted]2	[redacted]%	[redacted]	-[redacted]%
Proportion of patients receiving subsequent therapies: base case = EV+PEM arm 30.5%, Plat+Gem arm 48%					
10	Subsequent therapies are recalculated as a proportion of patients who had progressed (EV+PEM 60.5%, Plat+Gem 69.4%)	[redacted]2	-[redacted]%	[redacted]	[redacted]%
Relative dose of pembrolizumab in later line: base case = 100%					
11	Pembrolizumab later line RDI = 92.3% (same as 1L)	[redacted]2	[redacted]%	[redacted]	-[redacted]%
Discount rate: base case = 5% on costs and outcomes					
12	3.5% on costs and outcomes	[redacted]2	-[redacted]%	[redacted]	[redacted]%
13	0% on costs and outcomes	[redacted]2	-[redacted]%	[redacted]	[redacted]%
ESC MVSA [a]					
1+2a		[redacted]2	[redacted]%	[redacted]	-[redacted]%
1+2a +3a +3b		[redacted]3	[redacted]%	[redacted]	-[redacted]%
1+2a +3a +3b + 4		[redacted]3	[redacted]%	[redacted]	-[redacted]%
1+2a +3a +3b + 4 + 5		[redacted]3	[redacted]%	[redacted]	-[redacted]%
1+2a +3a +3b + 4 + 5 +6		[redacted]3	[redacted]%	[redacted]	-[redacted]%
1+2a +3a +3b + 4a + 5 +6		[redacted]3	[redacted]%	[redacted]	-[redacted]%
1+2a +3a +3b + 4 + 5 + 6 + 7		[redacted]3	[redacted]%	[redacted]	-[redacted]%

Source: generated during the evaluation from the economic model spreadsheet.

1L = First line; EV = Enfortumab vedotin; Gem = Gemcitabine; ICER = Incremental cost-effectiveness ratio; KM = Kaplan-Meier; MBS = Medicare Benefits Schedule; OS = Overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PD = Progressed disease; PEM = Pembrolizumab; PF = Progression-free; Plat = Platinum-based chemotherapy; QALY = Quality-adjusted life-year; RDI = relative dose intensity.

[a] Calculated during the preparation of the ESC advice

The redacted values correspond to the following ranges

1 $75,000 to < $95,000

2 $155,000 to < $255,000

3 $255,000 to < $355,000

6.56 In the submission's base case, the combined cost of EV+PEM required to achieve an ICER of $75,000 to < $95,000/QALY was $[redacted] (discounted). The submission stated an undiscounted EV+PEM treatment cost of $[redacted] would be required; however, this is not the undiscounted cost of EV+PEM, but rather the cost of EV+PEM required to achieve an ICER of $75,000 to < $95,000/QALY in an undiscounted model (i.e., all costs in the model are undiscounted). The ESC noted that removing discounting from the treatment cost of EV+PEM increased the cost per patient by about [redacted]%.

6.57 The ESC considered a revised model that was based on a time horizon of 10 years, incorporated background mortality, increased the age in the model to 72 years, increased the use of observed KM data (applying the Gebski method to determine truncation point for OS and PFS), removed terminal care costs and applied the log-logistic function to extrapolate EV time on treatment would provide a reasonable respecified base case model. The resulting ICER increased to $255,000 to < $355,000 per QALY gained, and the combined cost of EV+PEM required to achieve an ICER of $75,000 to < $95,000 reduced to $95,000 to < $115,000. The ESC noted the results of the respecified base case model are based on using 50% of the published prices of avelumab and PEM (2L). The ESC noted that, using the respecified base case model, the ICER increased to $255,000 to < $355,000 per QALY using a time horizon of 7.5 years and using alternative utility values increased to $255,000 to < $355,000 per QALY.

6.58 The pre-PBAC response proposed a revised base case model based on a time horizon of 10 years, incorporated background mortality, increased the age in the model to 72 years, updated MBS fees and increased the use of observed KM data (applying the Gebski method to determine truncation point for OS and PFS). The pre-PBAC response stated the revised base case resulted in an ICER of $255,000 to < $355,000 per QALY gained, with the (discounted) combined cost of EV+PEM required to achieve an ICER of $75,000 to < $95,000 [19].

[19] A revised economic model spreadsheet was not provided with the pre-PBAC response

EV+PEM cost/patient/course

Table 14: Drug cost per patient for proposed and comparator drugs, based on published prices.

	Proposed drug Trial dose and duration	Proposed drug Model	Proposed drug Financial estimates	Comparator Trial dose and duration	Comparator Model	Comparator Financial estimates
Mean dose	EV: not provided PEM: 184.6mg	EV: 80.1mg PEM: 184.6mg	EV: 95 mg PEM: 200 mg	Not provided	Cis:137mg Carbo:450mg Gem: 1580mg	Cis: 132 mg Carbo:329 mg Gem: 1880 mg
Mean duration	EV: 36.35 weeks PEM: 41.83 weeks	EV: 59.92 weeks PEM: 52.05 weeks	EV: 59.42 weeks PEM: 51.55 weeks	15.74 weeks	16.47 weeks	15.97 weeks
Cost/patient/month	-	EV: $[redacted] PEM: $[redacted]	EV: $[redacted] PEM: $[redacted]	-	$403.43	Gem-cis: $673 Gem-carbo: $662
Cost/patient/course	-	EV: $[redacted] PEM: $[redacted] Total: $[redacted]	EV: $[redacted] PEM: $[redacted] Total: $[redacted]	-	$1,540	Gem-cis: $2,473 Gem-carbo: $2,432

Source: compiled during the evaluation from the "Attachment 3.1 EV and PEM cost effectiveness model" and "Attachment 4.1 EV and PEM budget impact model" workbooks included in the submission.
Carbo = Carboplatin; Cis = Cisplatin; EV = enfortumab vedotin; Gem = Gemcitabine; PEM = pembrolizumab
Note: Mean doses were rounded up based on the assumption of no vial sharing in the financial analysis. Duration of treatment with EV, PEM and Plat+Gem in EV-302 were converted from months to weeks (months / 12 x 365.25 / 7).
Note: the estimates provided in Table 14 above are based on proposed published prices for EV+PEM. The cost/patient/course for EV+PEM reflects the undiscounted cost per patient using published prices. The submission proposed a combined effective price of EV+PEM to achieve an ICER $75,000 to < $95,000.

6.59 The PBAC noted the mean duration of treatment for EV was 71.64 weeks and for PEM was 51.42 weeks using the respecified ESC economic model (see paragraph 6.57).

Estimated PBS usage & financial implications

6.60 This submission was not considered by DUSC. The submission presented an epidemiological approach to estimate the extent of use and financial implications of listing EV+PEM for the first-line treatment of locally advanced or metastatic urothelial carcinomas. The key inputs utilised in the financial analysis are summarised in Table 15.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Bladder cancer		
Incidence	Yr 1: 3,261; Yr 2: 3,334; Yr 3: 3,408; Yr 4: 3,483; Yr 5: 3,561; Yr 6: 3,640; based on AIHW cancer projections for 2020-2023.[20] A growth rate of 2.2% was calculated and applied to project the incidence across the first 6 years of listing.	This was reasonable.
% that is urothelial carcinoma	93.7%; Table 15, Avelumab Public Summary Document, March 2021 PBAC meeting.	This was previously accepted by the PBAC and is reasonable.

[20] Australian Institute of Health and Welfare (AIHW). Cancer Data in Australia. Canberra: AIHW.2023.

Parameter	Value applied and source	Comment
% late stage at diagnosis (Locally advanced (Stage III) + metastatic disease (Stage IV))	12.67%; SEER stage distribution incidence data, 2012-2021 [21]	This was consistent with published literature and was reasonable.
% that is in situ at diagnosis (Stage 0a and 0is)	50.47%; SEER stage distribution incidence data, 2012-2021	This was consistent with published literature and was reasonable.
% of in situ carcinomas that progress post-BCG treatment	35.15%; van Gils-Gielen, Witjes et al. (1995)[22]	This input was highly uncertain with published literature reporting progression rates as low as 9.8% [23] [24].
% localised at diagnosis (Stage I and II)	36.86%; SEER stage distribution incidence data, 2012-2021	This appears to be consistent with published literature and is reasonable.
% of localised disease that has distant recurrence post-cystectomy	35%, Bilim, Kuroki et al. (2022) [25]	This input is highly uncertain with published literature reporting recurrence rates of 22-54% [26]. The PSCR) acknowledged the uncertainty but noted this input was within the range of the published estimates.
Renal pelvis and ureteral cancer		
Renal pelvis incidence	Yr 1: [redacted]^2; Yr 2: [redacted]^2; Yr 3: [redacted]^2; Yr 4: [redacted]^2; Yr 5: [redacted]^2; Yr 6: [redacted]^2; based on AIHW cancer incidence projections for 2020-2023 and a growth rate of 1.6%.	This was reasonable.
Ureteral incidence	Yr 1: [redacted]^2; Yr 2: [redacted]^2 Yr 3: [redacted]^2; Yr 4: [redacted]^2; Yr 5: [redacted]^2; Yr 6: [redacted]^2; based on AIHW cancer incidence projections for 2020-2023 and a growth rate of 2.4%.	This was reasonable.
% that is urothelial carcinoma	87%; Table 15, Avelumab Public Summary Document, March 2021 PBAC meeting.	This was previously accepted by the PBAC and was reasonable.

[21] National Cancer Institute. Urinary Bladder (Invasive & In Situ) Stage Distribution of SEER Incidence Cases, 2012-2021. Available from: https://seer.cancer.gov/statistics-network/explorer/application.html?site=71&data_type=1&graph_type=4&compareBy=sex&chk_sex_1=1&race=1&age_range=1&advopt_precision=1&advopt_show_count=on&hdn_view=1&advopt_show_apc=on&advopt_display=1#resultsRegion1.

[22] van Gils-Gielen RJ, Witjes WP, Caris CT, Debruyne FM, Witjes JA, Oosterhof GO. Risk factors in carcinoma in situ of the urinary bladder. Dutch South East Cooperative Urological Group. Urology. 1995 Apr;45(4):581-6.

[23] Tang DH, Chang SS. Management of carcinoma in situ of the bladder: best practice and recent developments. Ther Adv Urol. 2015 Dec;7(6):351-64.

[24] Mari A, Campi R, Tellini R, Gandaglia G, Albisinni S, Abufaraj M, et al. Patterns and predictors of recurrence after open radical cystectomy for bladder cancer: a comprehensive review of the literature. World J Urol. 2018 Feb;36(2):157-70.

[25] Bilim V, Kuroki H, Shirono Y, Murata M, Hiruma K, Tomita Y. Advanced Bladder Cancer: Changing the Treatment Landscape. J Pers Med. 2022 Oct 20;12(10).

[26] Özbir S, Girgin C, Kara C, Dinçel Ç. Local and systemic recurrence patterns of urothelial cancer after radical cystectomy. The Kaohsiung Journal of Medical Sciences. 2014 2014/10/01/;30(10):504-9.

Parameter	Value applied and source	Comment
% late stage at diagnosis (regional (Stage III) and metastatic disease (Stage IV))	68.68%; SEER stage distribution incidence data, 2012-2021 [27]	This was consistent with published literature and was reasonable.
% localised at diagnosis (early stages)	31.14%; SEER stage distribution incidence data, 2012-2021	This was consistent with published literature and was reasonable.
% of localised disease that have distant recurrence post RNU	16.64%, Tanaka, Kikuchi et al. (2014) [28]	The proportion of patients that are likely to have distant metastasis post RNU remains uncertain with published literature identifying rates of 10-20% [29].
Urethral cancer		
Incidence	Yr 1: [redacted][1]; Yr 2: [redacted][1]; Yr 3: [redacted][1]; Yr 4: [redacted][1]; Yr 5: [redacted][1]; Yr 6: [redacted][1]; based on AIHW cancer incidence projections for 2020-2023 and a growth rate of 3.3%.	This was reasonable.
% that is urothelial carcinoma	42%; Table 15, Avelumab Public Summary Document, March 2021 PBAC meeting.	This was previously accepted by the PBAC and was reasonable.
% late stage at diagnosis (regional (Stage III) and metastatic disease (Stage IV))	68.68%; SEER stage distribution incidence data, 2012-2021	This was consistent with published literature and was reasonable.
% localised at diagnosis (early stages)	31.14%; SEER stage distribution incidence data, 2012-2021	This was consistent with published literature and was reasonable.
% of localised disease that have distant recurrence post RNU	16.64%, Tanaka, Kikuchi et al. (2014)	The proportion of patients that are likely to have distant metastasis post RNU remains uncertain with published literature identifying rates of 10-20%.

[27] National Cancer Institute. Renal Pelvis Stage Distribution of SEER Incidence Cases, 2012-2021. Available from: https://seer.cancer.gov/statistics-network/explorer/application.html?site=640&data_type=1&graph_type=4&compareBy=sex&chk_sex_1=1&race=1&age_range=1&advopt_precision=1&advopt_show_count=on&hdn_view=1&advopt_show_apc=on&advopt_display=1#resultsRegion1.

[28] Tanaka N, Kikuchi E, Kanao K, Matsumoto K, Kobayashi H, Ide H, et al. Metastatic behavior of upper tract urothelial carcinoma after radical nephroureterectomy: association with primary tumor location. Ann Surg Oncol. 2014 Mar;21(3):1038-45.

[29] Locke JA, Hamidizadeh R, Kassouf W, Rendon RA, Bell D, Izawa J, et al. Surveillance guidelines based on recurrence patterns for upper tract urothelial carcinoma. Can Urol Assoc J. 2018 Aug;12(8):243-51.

Parameter	Value applied and source	Comment
Use and cost in eligible patients		
Eligibility for first-line therapy	90%, Table 15, Avelumab Public Summary Document, March 2021 PBAC meeting.	The DUSC has previously stated that 70% would be a reasonable estimate of first-line chemotherapy due to renal impairment and comorbidities in patients with UCs (paragraph6.67, Avelumab PSD, March 2021 PBAC meeting). However, given the claim of superior efficacy, assuming 90% of patients would be eligible for treatment with EV+PEM may be reasonable. Previously, the PBAC has considered that the proportion of patients who are treated with first-line PDC (90%) and the uptake rates proposed are largely uncertain and are likely to reflect the upper end of the range of use.
% electing treatment	[redacted]% in year 1 increasing to [redacted]% in year 6; assumption.	
Grandfathered patients	[redacted][1] in year 1	
Duration of EV+PEM treatment	59.42 weeks for EV, 51.55 weeks for PEM; based on mean treatment durations from the economic model.	The PBAC noted the mean treatment duration for EV and PEM would be different with the ESC respecified economic model (paragraph 6.59).
Duration of platinum-based chemotherapy	15.97 weeks for platinum-based chemotherapy; 74.18 weeks (17.12 months) for maintenance avelumab; based on mean treatment durations from the economic model.	While the treatment duration for platinum-based chemotherapy is reasonable, the duration of avelumab maintenance therapy is overestimated. The ESC considered it would be more appropriate to use an average treatment duration of 12.98 months for avelumab, consistent with the economic model (see further discussion in paragraph 6.75).
EV cost (per script)	$[redacted]; proposed DPMA based on AEMPs of $[redacted] for the 20 mg vial and $[redacted] for the 30 mg vial.	
PEM cost (per script)	$[redacted]; proposed DPMA based on AEMP of $[redacted] for the 100mg/4mL injection, 4mL vial	
Cisplatin cost (per script)	$159.19; weighted DPMA for PBS items 4319H, 7224F	The submission calculated the cost incorrectly as it did not utilise the most efficient combination of vials for the mean dose. This has been corrected in the evaluation, resulting in a weighted DPMA of $177.14.
Carboplatin cost (per script)	$154.48; weighted DPMA for PBS items 4309T, 722D	
Gemcitabine cost (per script)	$176.78; weighted DPMA for PBS items 4439P, 7246J	The submission calculated the cost incorrectly as it did not utilise the most efficient combination of vials for the mean dose. This has been corrected in the evaluation, resulting in a weighted DPMA of $191.38.
Avelumab	$5,620.77; weighted DPMA for PBS items 13122P, 13123Q, 13126W, 13132E; applied to 33.6% of patients.	

Parameter	Value applied and source	Comment
Subsequent treatments	Pembrolizumab: $7,864.88; weighted DPMA for PBS items 11646Y, 11632F; applied to 29.1% of patients. Duration of treatment: 9 weeks Enfortumab Vedotin [redacted]6,322.87[redacted] weighted DPMA for PBS items 13648H, 13634N; applied to 12.8% of patients. Duration of treatment: 28 weeks	The ESC noted the average duration of treatment for EV may be overestimated but noted it was consistent with the average duration applied in the economic model (see Table 9).
MBS costs	Not included.	This was not appropriate. Costs associated with IV administration should have been included in the submission (using MBS item 13950) for the proposed medicines, comparators and subsequent therapies. This has been done in the evaluation.

Source: Table 4-1, p117 of the submission.
AEMP = Approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; BCG = Bacillus Calmette Guerin; DPMA = Dispensed price for maximum amount; EV = Enfortumab vedotin; MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PEM = Pembrolizumab; PSD = Public summary document; RNU = radical nephroureterectomy; SEER = Surveillance, Epidemiology, and End Results; UCs = urothelial carcinomas
The redacted values correspond to the following ranges:
1 <500

6.61 Bladder, renal pelvis, ureteral and urethral cancer incidence projections for years 2020-2023 were sourced from the Australian Institute of Health and Welfare (AIHW) cancer data (2023) and growth rates of 2.2%, 1.6%, 2.4% and 3.3% were calculated for each cancer type, respectively. These growth rates were then applied to AIHW incidence projections in the previous year to estimate the incidence of these cancers across the first 6 years of listing. This was reasonable.

6.62 The submission estimated the total number of patients eligible for treatment with EV+PEM for each cancer type based on the inputs summarised in Table 15. 90% of patients were assumed to be eligible for first-line treatment with uptake rates of [redacted]% for EV+PEM across the first 6 years of listing. Alternate credible values for the inputs utilised in the submission were identified during the evaluation and tested in a sensitivity analysis.

6.63 The submission included <500 grandfathered patients in year 1 with treatment durations equal to half that of other eligible patients. The total number of patients treated with EV+PEM is presented in Table 16.

Table 16: Number of patients treated with EV+PEM

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Bladder cancer						
Incident patients (A)	3,261	3,334	3,408	3,483	3,561	3,640
Number of patients who are late stage at diagnosis (A x 93.7% x 12.67%)	387	396	405	414	423	432
Number of patients that progress post-BCG (from stage 0a, 0is) (A x 93.7% x 50.47% x 35.15%)	542	554	566	579	592	605
Number of patients with distant recurrence post-cystectomy (stage I+II) (A x 93.7% x 36.86% x 35%)	394	403	412	421	430	440
Renal pelvis cancer						
Incident patients (B)	348	353	358	364	370	375
No. of patients diagnosed at late stage (Stage III/IV) (B x 87% x 68.68%)	208	211	215	218	221	225
No. of patients with distance recurrence post RNU (Stage 0/I/II) (B x 87% x 31.14% x 16.64 %)	16	16	16	16	17	17
Ureteral cancer						
Incident patients (C)	186	190	195	200	204	209
No. of patients diagnosed at late stage (Stage III/IV) (C x 87% x 68.68%)	111	114	117	120	122	125
No. of patients with distance recurrence post RNU (Stage 0/I/II) (C x 87% x 31.14% x 16.64 %)	8	9	9	9	9	9
Urethral cancer						
Incident patients (D)	47	49	50	52	54	55
No. of patients diagnosed at late stage (D x 42% x 68.68%)	14	14	15	15	15	16
No. of patients with distance recurrence post RNU (Stage 0/I/II) (D x 42% x 31.14% x 16.64%)	1	1	1	1	1	1
Treated patients						
Total incident patients (E)	1,682	1,718	1,755	1,793	1,831	1,871
Patients eligible for first-line treatment with EV + PEM (E x 90%)	1,513	1,546	1,579	1,614	1,648	1,684
Total treated incident patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Grandfathered patients	[redacted][2]	-	-	-	-	-

Source: tabulated during the evaluation from Tables 4-3, 4-4, 4-5, 4-6 and 4-7, pp118-121 of the submission.
BCG = Bacillus Calmette-Guerin; RNU = radical nephroureterectomy
The redacted values correspond to the following ranges:
1 500 to < 5,000
2 <500

6.64 Treatment durations of 59.42 weeks and 51.55 weeks were derived from the mean time on treatment from the economic model for EV and PEM, respectively. For grandfathered patients, treatment durations of 29.71 weeks for EV and 25.78 weeks for PEM were applied. Based on compliance rates of 80.10% (EV) and 92.30% (PEM) from the EV-302 trial, the submission estimated that each patient would require 27.86

scripts per treatment year for EV[30] and 16.05 scripts per treatment year for PEM[31].

6.65 The submission assumed that the listing of EV+PEM would displace the first-line use of platinum-based chemotherapy (cisplatin or carboplatin) in combination with gemcitabine and reduce the use of second-line PEM and third-line EV. Finally, the submission assumed that there would be an increase in the second-line use of chemotherapy. However, the proportions of patients that go on to receive subsequent treatments remain uncertain and therefore, is it difficult to accurately ascertain the change in use of subsequent treatments.

6.66 The submission did not estimate any costs to the MBS. This is not reasonable. As the proposed drugs, comparators and subsequent treatments are all administered intravenously, costs for IV administration using MBS item 13950 will apply. The net

[30] Scripts per treatment year (EV) = 80.10% x 52.18 x dose per week (2/3 = 0.67)
[31] Scripts per treatment year (PEM) = 92.30% x 52.18 x dose per week (1/3 = 0.33)

cost to the MBS was calculated during the evaluation and is presented below.

6.67 The net financial implications of listing EV+PEM are presented in Table 17.

Table 17: Estimation use and financial implications of listing EV+PEM

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Increase in use of EV+PEM						
Total treated incident patients	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Grandfathered patients	[redacted]2	-	-	-	-	-
Patient years of treatment: EV [a]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patient years of treatment: PEM [b]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Total patient years of treatment	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
EV scripts [c]	[redacted]3	[redacted]3	[redacted]4	[redacted]4	[redacted]4	[redacted]5
PEM scripts [d]	[redacted]6	[redacted]6	[redacted]7	[redacted]7	[redacted]7	[redacted]7
Total EV+PEM scripts	[redacted]5	[redacted]5	[redacted]8	[redacted]8	[redacted]9	[redacted]9
Estimated financial implications of EV+PEM						
Cost of EV to the PBS/RPBS less copays	[redacted]10	[redacted]10	[redacted]11	[redacted]11	[redacted]11	[redacted]11
Cost of PEM to the PBS/RPBS less copays	[redacted]10	[redacted]10	[redacted]10	[redacted]10	[redacted]10	[redacted]10
Total cost of EV+PEM to the PBS/RPBS less copays	[redacted]12	[redacted]12	[redacted]12	[redacted]13	[redacted]13	[redacted]13
Change in use of comparator and subsequent treatments						
Total incident patients (A)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patients eligible for first-line treatment with PDC (A) x 90%	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Incident treated patients	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Total patient years of treatment	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Reduction in 1L PDC scripts	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]7	[redacted]7
Reduction in avelumab scripts	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6
Reduction in 2L PEM scripts	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Reduction in 3L EV scripts	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Increase in 2L PDC scripts	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Total reduction in scripts [e]	[redacted]7	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]4
Estimated financial implications of comparators and subsequent treatments						
Cost offsets to PBS/RPBS less copays: 1L PDC	[redacted]14	[redacted]14	[redacted]14	[redacted]14	[redacted]14	[redacted]14
Cost offsets to PBS/RPBS less copays: avelumab	[redacted]15	[redacted]16	[redacted]16	[redacted]17	[redacted]10	[redacted]10
Cost offsets to PBS/RPBS less copays: 2L PEM	[redacted]14	[redacted]14	[redacted]14	[redacted]14	[redacted]14	[redacted]14
Cost offsets to PBS/RPBS less copays: 3L EV	[redacted]18	[redacted]18	[redacted]18	[redacted]18	[redacted]18	[redacted]18
Cost to PBS/RPBS less copays: 2L PDC	[redacted]14	[redacted]14	[redacted]14	[redacted]14	[redacted]14	[redacted]14
Total reduction in cost to the PBS/RPBS less copays [f]	[redacted]19	[redacted]10	[redacted]10	[redacted]10	[redacted]10	[redacted]10
Net financial implications of listing EV+PEM						
Net cost to PBS/RPBS	[redacted]11	[redacted]11	[redacted]11	[redacted]11	[redacted]12	[redacted]1212
Net cost to MBS [g]	[redacted]14	[redacted]14	[redacted]14	[redacted]14	[redacted]14	[redacted]14
Net cost to PBS/RPBS and MBS	[redacted]11	[redacted]11	[redacted]11	[redacted]11	**12**	[redacted]12
Pre-PBAC response						
Net cost to PBS/RPBS[h]	[redacted]11	[redacted]11	[redacted]12	[redacted]12	[redacted]12	[redacted]12

Source: compiled during the evaluation from the "Attachment 4.1 EV and PEM budget impact model" workbook included in the submission and from Table 2 pre-PBAC response

1L = First-line; 2L = Second-line; 3L = Third-line; copays = copayments; EV = Enfortumab vedotin; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PDC = Platinum-doublet chemotherapy; PEM = Pembrolizumab; RPBS = Repatriation Schedule of Pharmaceutical Benefits

[a] Included 9 grandfathered patient years of treatment in year 1.

[b] Included 7 grandfathered patient years of treatment in year 1.

[c] Based on scripts per treatment year of 27.86 per patient.

[d] Based on scripts per treatment year of 16.05 per patient.
[e] Based on scripts per treatment year of 15.91, 27.48, 17.39, 24.8, 16.06 and 31.35 for cisplatin, gemcitabine, carboplatin, avelumab, pembrolizumab and enfortumab vedotin, respectively.
[f] Revised estimates are based on the correct cost for cisplatin ($177.14) and gemcitabine ($191.38), based on the efficient combination of vials.
[g] Calculated during the evaluation for all drugs administered intravenously using MBS item 13950 ($123.05, 80% benefit).
[h] A revised financial estimates spreadsheet was not provided with the pre-PBAC response
The redacted values correspond to the following ranges:
1 500 to < 5,000
2 <500
3 30,000 to < 40,000
4 40,000 to < 50,000
5 50,000 to < 60,000
6 10,000 to <20,000
7 $20 million to <$30 million
8 60,000 to < 70,000
9 70,000 to < 80,000
10 $100 million to < $200 million
11 $200 million to < $300 million
12 $300 million to < $400 million
13 $400 million to < $500 million
14 $0 to < $10 million
15 $50 million to < $60 million
16 $80 million to < $90 million
17 $90 million to < $100 million
18 $10 million to < $20 million
19 $70 million to < $80 million

6.68 Based on the published prices of EV and PEM *(*i.e., resulting in an ICER of $155,000 to < $255,000 per QALY), the cost of listing EV + PEM on the PBS/RBPS is estimated to be $400 million to < $500 million in Year 6, and a total of > $1 billion the first 6 years of listing. Based on the undiscounted cost per patient per course outlined in paragraphs 6.57 and 6.58 (i.e, resulting in an ICER of $75,000 to < $95,000 per QALY), the cost over 6 years would be approximately > $1 billion[32].

6.69 The total net cost to the PBS/RPBS and MBS of listing EV+PEM was estimated to be $300 million to < $400 million in Year 6, and a total of > $1 billion in the first 6 years of listing, based on the published prices for the proposed, comparator and subsequent treatment drugs. The treatment durations of subsequent avelumab and third-line EV are longer than what has been previously accepted by the PBAC and as such the cost offsets may have been overestimated. Further, there is uncertainty regarding the proportions of patients who receive avelumab maintenance therapy and 2L PEM. Thus, the net cost to the PBS/RPBS, as estimated in the submission, is largely uncertain.

6.70 The financial estimations were highly sensitive to several inputs that were identified as areas of uncertainty during the evaluation. In addition to the sensitivity analyses presented in the submission, alternate treatment durations for avelumab maintenance therapy and third-line EV, as well as alternate credible values for progression rates of carcinoma in situs and localised disease for each cancer type were

[32] Calculated as ($[redacted]/$[redacted]) x cost over 6 years

identified during the evaluation (Table 18). Further, the submission assumed that all patients who are eligible for treatment with EV+PEM would have otherwise received first-line chemotherapy. However, the DUSC has previously stated that 70% is a more reasonable estimate of eligibility for first-line chemotherapy while the PBAC noted that 90% likely reflected the upper end of use of 1L platinum-doublet chemotherapy (PDC) and that the proportion of patients who receive 1L PDC is uncertain (paragraph 6.67 and 7.11, Avelumab PSD, March 2021 PBAC meeting). The PSCR stated that patient eligibility for platinum-based chemotherapy is determined based on ECOG performance status and comorbidities with EV+PEM having fewer contraindications to treatment. As such, the PSCR argued that the higher estimate of 90% eligibility for treatment with EV+PEM, and consequently for the cost offsets associated with the first-line use of chemotherapy were justified. The ESC noted the potential for differences in eligibility for treatment between EV+PEM and platinum-based chemotherapy due to contraindications and considered that, while 90% eligibility for EV+PEM might be reasonable, it may not be appropriate to assume all patients eligible for treatment with EV+PEM would otherwise have received platinum-based chemotherapy. The ESC considered that in terms of cost offsets it may be more appropriate to assume that 70% of all incident patients would otherwise have received platinum-based chemotherapy. The ESC noted this would impact on the cost offsets for AVEL, PEM and EV as they are used after PDC. The pre-PBAC response agreed with the ESC that it would be appropriate to assume that 70% of all incident patients would otherwise have received platinum-based chemotherapy and incorporated this approach in the revised estimates provided.

Table 18: Results of the univariate sensitivity analyses

Net cost to the PBS and RPBS	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	% change from baseline
Base case	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]2	[redacted]2	-
Stage distribution (base case: SEER incidence data, 2012-2021)							
David, Mallin et al. (2009) [33]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	-9%
Uptake rate of EV+PEM							
+5%/year	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]2	[redacted]2	5%
-5%/year	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	-6%
Proportion of la/mUC patients eligible for first-line treatment (base case: EV+PEM = 90%, PBC = 90%)							
85% (EV+ PEM & PBC)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	-5%
90% (EV+PEM), 70% (PBC)	[redacted]1	[redacted]1	[redacted]1	[redacted]2	[redacted]2	[redacted]2	9%
Progression post-BCG of CIS bladder cancer (base case: 35.15%)							
9.8%	[redacted]3	[redacted]3	[redacted]1	[redacted]1	[redacted]1	[redacted]1	-30%
13.9%	[redacted]3	[redacted]3	[redacted]1	[redacted]1	[redacted]1	[redacted]1	-24%
Distant recurrence of localised bladder cancer post cystectomy (base case: 35%)							
22%	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	-9%
45%	[redacted]1	[redacted]1	[redacted]1	[redacted]2	[redacted]2	[redacted]2	6%
54%	[redacted]1	[redacted]1	[redacted]1	[redacted]2	[redacted]2	[redacted]2	11%
Distant metastasis post-RNU in patients with localised renal pelvis, ureteral and urethral cancers (base case: 16.64%)							
10%	[redacted]1	[redacted]1	[redacted]11	[redacted]1	[redacted]2	[redacted]2	-1%
20%	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]2	[redacted]2	-

Source: tabulated during the evaluation, from Table 4-19, p128 of the submission and from the "Attachment 4.1 EV and PEM budget impact model" workbook included in the submission.

3L = Third line; CI = Confidence interval; CIS = Carcinoma in situ; EV = Enfortumab vedotin; PBC = platinum-based chemotherapy; PBS = Pharmaceutical Benefits Scheme; PEM = Pembrolizumab; RPBS = Repatriation Schedule of Pharmaceutical Benefits; SEER = Surveillance, Epidemiology, and End Results; la/mUC = Locally advanced or metastatic urothelial cancer

[a] Calculated during the preparation of the ESC advice

The redacted values correspond to the following ranges:

1 $200 million to < $300 million

2 $300 million to < $400 million

3 $100 million to < $200 million

6.71 The evaluation noted that the number of treated patients is sensitive to the rates of progression to distant metastases in carcinoma in situs and localised bladder cancer. The PSCR acknowledged the challenges associated with accurately calculating the number of la/mUC patients in Australia and argued that with the paucity of data to support more definitive values the progression rates were reasonable.

6.72 The evaluation also noted the net cost to the PBS/RPBS is moderately sensitive to the duration of subsequent treatment with third-line EV and highly sensitive to the duration of treatment of avelumab maintenance therapy. The PSCR noted that EV-301 data was used to support the duration of subsequent treatment with EV monotherapy in the third line setting and argued that this was reasonable in light of the small proportion of patients who had progressed to third-line in the EV-302 trial. In addition,

[33] David KA, Mallin K, Milowsky MI, Ritchey J, Carroll PR, Nanus DM. Surveillance of urothelial carcinoma. Cancer. 2009;115(7):1435-47.

the PSCR noted the duration of subsequent avelumab treatment is based on trial data from EV-302 and argued that this more representative of use in this population than using an external source of data. The ESC considered the duration of treatment for third-line EV may be overestimated but noted it was consistent with the duration used in the economic model. The pre-PBAC response proposed that the duration of treatment for avelumab and for third-line EV should be consistent with the economic model.

6.73 The ESC noted the average duration of avelumab treatment was calculated using the Weibull extrapolation of the time on treatment curve as applied in the economic model. However, it did not account for capping by the PFS curve (as described in paragraph 6.43). The ESC considered it would be more appropriate to use an average treatment duration of 12.98 months, consistent with the economic model.

6.74 The ESC noted the number of patients treated with avelumab, PEM and EV was provided by the DUSC Secretariat (Table 19). Data was extracted to 31 August for PBS item codes 11632F, 11646Y, 13122P, 13123Q, 13126W, 13132E, 13634N and 13648H based on the date of supply.

Table 19: Number of incident patients treated (as per data provided by DUSC Secretariat)

	Pembrolizumab	Avelumab	Enfortumab vedotin
First PBS listed	1 March 2019	1 October 2022	1 October 2023
2019	485	-	-
2020	467	-	-
2021	438	-	-
2022	363	176	-
2023	312	273	-
2024	222 [a]	225 [a]	293 [b]

Source: Complied during the preparation of the ESC advice

[a] To 31 August 2024

[b] 1 October 2023 to 21 August 2024

6.75 The ESC noted that the cost offsets in the financial estimates in Year 1 accounted for 407 patients who would have received avelumab (33.6% x 1,211), 352 patients who would have received PEM (29.1% x 1,211) and 155 who would have received EV (12.8% x 1,211). The ESC noted the estimates for avelumab and PEM were significantly higher than the total number of patients treated in 2023.

6.76 The ESC noted using the total number of treated patients for avelumab and PEM in 2023 was 585 (312 + 273) and assuming this represented 62.7% (33.6% + 29.1%) of the population that would be treated with EV + PEM, resulted in an estimated number of patients of 933 (585/62.7%). The ESC noted this was significantly lower than estimated in the submission (500 to < 5,000) which suggests that the patient numbers were substantially overestimated. The pre-PBAC response argued that a retrospective cohort study from the United States reported the uptake of second-line therapy to be

low, with only 37.7% of patients receiving such therapy between 2016 and 2023.[34] The pre-PBAC response went on to argue that if the use of pembrolizumab between 2019 and 2021 represents 37.7% of the first line population the submission assumptions regarding the number of incident treated patients were reasonable. The PBAC did not agree with the argument proposed in the pre-PBAC response and instead considered that, based on triangulation of data provided by the DUSC Secretariat, the number of incident treated patients was substantially overestimated.

6.77 The pre-PBAC response provided revised financial estimates (see Table 17). The pre-PBAC response indicated the revised estimates included no changes to the number of incident treated patients, updated cost offsets based on 70% of the first line population being eligible for Plat+Gem compared to 90% being eligible for EV+PEM and assumed treatment durations of subsequent avelumab and third-line EV were consistent with the economic model.

Quality Use of Medicines

6.78 The sponsor stated that they are actively engaged in education activities that support the safe use of EV+PEM in Australian clinical practice with routine pharmacovigilance activities being conducted. The sponsor did not identify any QUM issues and no QUM issues were identified during the evaluation.

Risk sharing arrangements

6.79 The submission did not propose a risk sharing arrangement (RSA) for EV+PEM. The PBAC noted there are RSAs in place for PEM, EV and AVEL in this indication, with the RSAs for EV and AVEL designed to achieve cost-effective prices.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing of enfortumab vedotin in combination with pembrolizumab (EV+PEM) for the first line treatment of locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer (la/mUC). The PBAC is satisfied that EV+PEM provides, for some patients, a significant improvement in efficacy over platinum based chemotherapy with gemcitabine (Plat+Gem). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of EV+PEM would be acceptable at the combined EV+PEM cost required to achieve an incremental cost-effectiveness ratio (ICER) of around $55,000 to < $75,000 per QALY gained and with a risk sharing arrangement that accounts for expenditure on the use

[34] Mathew Thomas V, Jo Y, Tripathi N, et al. Treatment Patterns and Attrition With Lines of Therapy for Advanced Urothelial Carcinoma in the US. *JAMA Netw Open.* 2024;7(5): e249417. doi:10.1001/ jamanetworkopen.2024. 941

of first line and subsequent line therapies.

7.2 The PBAC noted the input from individuals, health care professions and organisations that highlighted the benefits of EV+PEM in terms of overall survival and response rates in this poor prognosis cancer. The PBAC also noted the support for EV+PEM for this indication from the Medical Oncology Group of Australia (MOGA). The PBAC acknowledged the high clinical need for more effective therapies for la/mUC, noting that overall the current PBS-listed therapies are moderately effective.

7.3 With regard to the requested listing and restriction, the PBAC advised that:

- An Authority Required (STREAMLINED) listing was appropriate.
- The clinical criteria referring to neoadjuvant/adjuvant chemotherapy did not require specification of a time frame for recurrence from completion of therapy (see paragraph 3.3).
- The Secretariat addition of administrative advice regarding pseudoprogression in the pembrolizumab restriction was not required.
- Flow on changes were required to prevent retreatment with enfortumab vedotin in the third-line setting. The PBAC noted the current restrictions for avelumab and pembrolizumab already include criterion that precludes retreatment.

7.4 The PBAC considered the proposed comparator of Plat+Gem was appropriate.

7.5 The primary clinical evidence supporting the clinical claim was the EV-302 trial comparing EV+PEM versus Plat+Gem in previously untreated la/mUC patients. The PBAC noted that in the Plat+Gem arm, 30.4% of patients received avelumab maintenance therapy and agreed with the ESC this is likely to be less than what is observed in the Australian clinical setting. In addition, the PBAC noted the average age of patients in the EV-302 trial was younger than the average of bladder cancer patients in the Australian setting (67.9 years versus 75.3 years respectively). In terms of the results of the EV-302 trial, the PBAC noted that EV+PEM demonstrated a substantial improvement in progression free survival (PFS) by blinded independent central review (BICR) in the ITT population compared to Plat+Gem (HR=0.45; 95% CI: 0.38, 0.54) with an incremental gain in median PFS of 6.2 months. The PBAC also considered the improvement in overall survival (OS) was substantial with EV+PEM (HR=0.47; 95% CI: 0.38, 0.58) with an incremental gain in median OS of 15.4 months. The PBAC noted the benefit in PFS and OS was demonstrated in almost all prespecified subgroups including age (<65 and ≥ 65), but a subgroup analysis on the impact of maintenance therapy with avelumab was not included. The PBAC considered the claim of superior comparative effectiveness was supported by the evidence presented. However, the PBAC considered the magnitude of benefit observed in the EV-302 trial may not be realised in the proposed PBS population due to differences in age, performance status and the use of subsequent therapies (including maintenance avelumab).

7.6 The PBAC noted the claim of superior safety made in the submission based on exposure adjusted adverse event rates. The PBAC agreed with the evaluation and the ESC that use of the unadjusted rather than adjusted adverse events was appropriate in considering the comparative harms. The PBAC noted that EV+PEM had nearly double the rate of treatment emergent adverse events (TEAEs) leading to discontinuation (39.8% vs. 21.5%) and a higher rate of serious TEAEs (50.0% vs. 39.0%) compared to Plat+Gem. The PBAC considered that the claim of superior comparative safety was not adequately supported by the data. Instead the PBAC agreed with the ESC that a claim of inferior but manageable safety profile was appropriate.

7.7 The submission presented a cost-utility analysis to determine the cost-effectiveness of EV+PEM with the base case reporting an ICER of $155,000 to < $255,000 per QALY gained. The PBAC noted the economic model did not include proposed prices for EV+PEM, but instead back-calculated the combined treatment cost to achieve an ICER of $75,000 to < $95,000 per QALY. The PBAC noted the ESC proposed a respecified base case based on a time horizon of 10 years, that incorporated background mortality, increased the age in the model to 72 years, increased the use of observed KM data (applying the Gebski method to determine truncation point for OS and PFS), removed terminal care costs and applied the log-logistic function to extrapolate EV time on treatment. The PBAC noted the ESC respecified base case increased the ICER to $255,000 to < $355,000 per QALY gained, and that the combined cost of EV+PEM required to achieve an ICER of $75,000 to < $95,000 reduced from $95,000 to < $115,000 to $95,000 to < $115,000. The PBAC noted that the pre-PBAC response accepted the changes to the base case proposed by the ESC with the exception of the removal of terminal care costs and the application of the log-logistic function to extrapolate EV time on treatment. The PBAC considered the removal of terminal care costs as proposed by the ESC remained appropriate as there is no indication that EV+PEM results in a cure and there was a difference in the proportion of patients alive at the end of the modelled time horizon. The PBAC also accepted the ESC argument that the log-logistic function was the best statistical fit and appeared to fit the EV time on treatment data reasonably well. The PBAC therefore considered the respecified base case proposed by the ESC appropriate to determine the cost-effectiveness of EV+PEM. The PBAC also considered the proposed target ICER was too high and that an ICER of around $55,000 to < $75,000 per QALY gained (using the effective prices of AVEL and PEM 2L) was appropriate and consistent with relevant previous considerations. The PBAC noted that a reduction in the combined cost of EV+PEM would be required to achieve the ICER proposed by the Committee.

7.8 The PBAC noted the revised financial estimates presented in the pre-PBAC response and advised that they were overestimated with further amendments necessary to reflect the likely use in clinical practice. Specifically, the PBAC agreed with the ESC that triangulation of the number of patients treated with avelumab and later line PEM indicated that the estimated number of patients likely to be treated with EV+PEM was substantially overestimated. The PBAC recommended that the number of incident

treated patients in Table 16 be adjusted using the approach specified by the ESC in paragraph 6.76. The PBAC considered the inclusion of grandfathered patients as stated in the submission remained appropriate. The PBAC considered that updating the cost offsets based on 70% of the first line population being eligible for Plat+Gem compared to 90% being eligible for EV+PEM was appropriate. The PBAC also considered it was appropriate to assume treatment durations of subsequent avelumab (14.93 months) and third-line EV (6.46 months) were consistent with the respecified economic model. The PBAC noted that the financial estimates would also need to be updated for the outcome from the recommendations made by the Committee in paragraph 7.7. The PBAC considered the resulting financial estimates would be appropriate to form the basis of a risk sharing arrangement.

7.9 The PBAC noted that a risk sharing arrangement was not proposed in the submission but considered such an arrangement was appropriate given the very high and significant cost to the Commonwealth, noting also that the cost effectiveness of EV+PEM relies on cost offsets in the later line setting. The PBAC considered a combined risk sharing arrangement accounting for expenditure on first line and subsequent line use across EV and PEM would be appropriate. The PBAC also noted that as there would be expected offsets for AVEL, it would be preferred if AVEL was also captured in a shared risk sharing arrangement.

7.10 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for EV+PEM that:

a) EV+PEM is expected to provide a substantial and clinically relevant improvement in efficacy over Plat+Gem;

b) EV+PEM is expected to address a high and urgent unmet clinical need;

c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

7.11 The PBAC advised that this submission would not meet the criteria for an Independent Review as received a positive PBAC recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing listings as follows:

Enfortumab vedotin

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	№.of Rpts
ENFORTUMAB VEDOTIN Injection	NEW (Public) NEW (Private)	125mg	7

Available brands	
Padcev (enfortumab vedotin 30 mg injection, 1 vial)	
Padcev (enfortumab vedotin 20 mg injection, 1 vial)	
Restriction Summary [new] / Treatment of Concept: [new]	
	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.
Restriction Summary [new] / Treatment of Concept: [new]	
	Episodicity: n/a
	Severity: Locally advanced (Stage III) or metastatic (Stage IV)
	Condition: Urothelial cancer
	Indication: Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
	Clinical criteria:
	Patient must not have received prior systemic therapy for this condition at the initiation of treatment with this drug, with the exception of neoadjuvant/adjuvant chemotherapy.
	AND
	Clinical criteria:
	Patient must have/have had a WHO performance status score of no greater than 2 at treatment initiation with this drug.
	AND
	Treatment criteria:
	Patient must be undergoing combination therapy consisting of no more than 24 months of: (i) enfortumab vedotin, (ii) pembrolizumab; OR
	Patient must be undergoing monotherapy with this drug after exceeding a lifetime total of 24 cumulative months of combination therapy consisting of: (i) enfortumab vedotin, (ii) pembrolizumab, from the first administered dose; OR
	Patient must be undergoing monotherapy with this drug due to a contraindication/intolerance to pembrolizumab, requiring temporary/permanent discontinuation; document the details in the patient's medical records.
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this drug for the first time; OR
	Patient must be undergoing continuing treatment with this drug, with each of the following being true: (i) all other PBS eligibility criteria in this restriction are met, (ii) disease progression is absent.
Restriction Summary [new] / Treatment of Concept: [new]	

	Treatment Phase: Transitioning from non-PBS to PBS subsided treatment – 'Grandfather' arrangement
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this indication prior to [date of PBS listing],
	AND
	Clinical criteria:
	Patient must have/have had a WHO performance status score of no greater than 2 prior to initiation of non-PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition.
	AND
	Treatment criteria:
	Patient must be undergoing combination therapy consisting of no more than 24 months of: (i) enfortumab vedotin, (ii) pembrolizumab; OR
	Patient must be undergoing monotherapy with this drug after exceeding a lifetime total of 24 cumulative months of combination therapy consisting of: (i) enfortumab vedotin, (ii) pembrolizumab, from the first administered dose; OR
	Patient must be undergoing monotherapy with this drug due to a contraindication/intolerance to pembrolizumab, requiring temporary/permanent discontinuation; document the details in the patient's medical records;
	Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

Pembrolizumab

MEDICINAL PRODUCT Form	**PBS item code**	**Max. Amount**	**№.of Rpts**
PEMBROLIZUMAB Injection	NEW (Public) NEW (Private)	200 mg	3
Available brands			
Keytruda (pembrolizumab 100 mg/4 mL injection, 4 mL vial)			
Restriction Summary [new] / Treatment of Concept: [new]			
	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: n/a		
	Severity: Locally advanced (Stage III) or metastatic (Stage IV)		
	Condition: Urothelial cancer		
	Indication: Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer		
	Clinical criteria:		

	Patient must not have received prior systemic therapy for this condition at the initiation of treatment with this drug, with the exception of neoadjuvant/adjuvant chemotherapy,
	AND
	Clinical criteria:
	Patient must have/have had a WHO performance status score of no greater than 2 at treatment initiation with this drug.
	AND
	Treatment criteria:
	Patient must be undergoing combination therapy consisting of no more than 24 months of: (i) enfortumab vedotin, (ii) pembrolizumab; OR
	Patient must be undergoing monotherapy with this drug due to intolerance to enfortumab vedotin, requiring temporary/permanent discontinuation; document the details in the patient's medical records,
	AND
	Treatment criteria:
	Patient must not be undergoing continuous PBS-subsidised treatment where this benefit is extending treatment beyond 24 cumulative months from the first administered dose, once in a lifetime.
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this drug for the first time; OR
	Patient must be undergoing continuing treatment with this drug, with each of the following being true: (i) all other PBS eligibility criteria in this restriction are met, (ii) disease progression is absent.
Restriction Summary [new] / Treatment of Concept: [new]	
	Indication: Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
	Treatment Phase: Transitioning from non-PBS to PBS subsided treatment – 'Grandfather' arrangement
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this indication prior to [date of PBS listing],
	AND
	Clinical criteria:
	Patient must have/have had a WHO performance status score of no greater than 2 prior to initiation of non-PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition.
	AND
	Treatment criteria:
	Patient must be undergoing combination therapy consisting of no more than 24 months of: (i) enfortumab vedotin, (ii) pembrolizumab; OR
	Patient must be undergoing monotherapy with this drug due to intolerance to enfortumab vedotin, requiring temporary/permanent discontinuation; document the details in the patient's medical records,
	AND
	Treatment Criteria:
	Patient must not be undergoing treatment with this drug beyond 24 cumulative months from the first administered dose, once in a lifetime.
	Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only.

	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

Flow-ons

For current PBS item codes in the 3rd line setting (13634N and 13648H) add the following CC to prevent retreatment with enfortumab vedotin in this setting.

	Clinical Criteria
	Patient must not have received prior treatment with this drug for this condition.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

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

10 Sponsor's Comment

Astellas Pharma Australia are thrilled with the PBAC recommendation and will do everything possible in the coming months to speed the PBS Listing.