6.15 PEMBROLIZUMAB, Solution concentrate for I.V. infusion 100 mg in 4 mL, Keytruda®, Merck Sharp & Dohme (Australia) Pty Ltd

1 Purpose of Submission

1.1 To consider a submission from Merck Sharp & Dohme for a multi-indication (broad) listing for pembrolizumab in advanced or metastatic cancers.

2 Background

Previous PBAC considerations

2.1 The PBAC's most recent consideration of a multi-indication listing for PD-(L)1 inhibitors was at the September 2024 meeting. Prior to this the PBAC had considered a submission in December 2023. Previous PBAC considerations are outlined in the September 2024 and December 2023 minutes.

2.2 The PBAC was supportive of implementing simplified listings for PD-(L)1 inhibitors if this would facilitate appropriate and timely access for patients and reaffirmed its previous advice, that in the context of the extensive experience with applications for PD-(L)1 inhibitors, it would be appropriate and desirable to have a simplified process for listing future indications.

2.3 The PBAC remain concerned about patient access to PD-(L)1 inhibitors for ultra-rare tissue types and the resulting unmet clinical need. The PBAC noted that some ultra-rare tissue types were not dMMR/MSI-H or TMB-H and consequently did not have (and were unlikely to have) a registered TGA indication.

2.4 The PBAC noted that the financial estimates for any multi-indication listing would inherently have a high degree of uncertainty. Any proposal for a multi-indication listing should include a Risk sharing Arrangement (RSA) that provided confidence regarding the budget impact.

2.5 The PBAC advised that any multi-indication arrangement should not disadvantage or exclude other PD-(L)1 inhibitors and ensure that access to indications where PD-(L)1 inhibitors are used in combination with other high-cost agents is not affected. The PBAC noted a PBS listing which provided access to one of the components of a combination regimen ahead of the other(s) would be problematic.

3 Outline of July 2025 Proposal

3.1 This submission proposed a single weighted, effective approved ex-manufacturer price (AEMP) for pembrolizumab based on existing listed indications. A price volume arrangement (PVA) is proposed with increasing rebate levels over 4 tiers. The prices and tiers of the current and September 2024 proposals are provided at Table 1.

Table 1: Comparison of tier structure and proposed prices, previous and current submissions

Submission Q4 2023			Current submission		
Structure	**AEMP[1] per 100 mg**	**pro rata price[1,2] q4w**	**Structure**	**AEMP per 100 mg**	**pro rata price[1,2] q4w**
Tier 1 current indications (early and advanced and metastatic)	$[redacted]	$[redacted]	**Tier 1 current indications (advanced and metastatic)**	$[redacted]	$[redacted]
Tier 2 TGA approved no PBS subsidy	$[redacted]	$[redacted]	**Tier 2 all future adv/met indications**	$[redacted]	$[redacted]
Tier 3 planned TGA submissions	$[redacted]	$[redacted]	**Tier 3 retreatment ToT > 2 years**	$[redacted]	$[redacted]
Tier 4 ultra-rare cancers	$[redacted]	$[redacted]	**Tier 4 'allowance'**	$[redacted]	$[redacted]

Adv = advanced; AEMP = approved ex-manufacturer price; met = metastatic; q4w = every 4 weeks; PBS = Pharmaceutical Benefits Scheme; TGA = Therapeutic Goods Administration; ToT = time on treatment.
1 Year-1 price
2 pro rata price per 4 weeks, based on the standard dose of 200 mg q3w

3.2 The pre-PBAC response provided an updated proposal with the following price structures as options for the PBAC to consider. Changes to the weighted price reflected updates to the methodology used to derive this price based on comments from the Secretariat:

Table 2: Revised tier and pricing options from pre-PBAC response

Pre-PBAC response (4 Tier structure)			Pre-PBAC response (3 Tier structure)		
Structure	**AEMP per 100 mg**	**pro rata price[2] q4w**	**Structure**	**AEMP per 100 mg**	**pro rata price[2] q4w**
Tier 1 current indications (advanced and metastatic)	$[redacted]	$[redacted]	**Tier 1 current indications (advanced and metastatic)**	$[redacted]	$[redacted]
Tier 2 all future adv/met indications	$[redacted]	$[redacted]	**Tier 2 all future adv/met indications**	$[redacted]	$[redacted]
Tier 3 retreatment ToT > 2 years	$[redacted]	$[redacted]	**Tier 3 retreatment ToT > 2 years and RSA 'allowance'**	$[redacted]	$[redacted]
Tier 4 'allowance'	$[redacted]	$[redacted]			

Adv = advanced; AEMP = approved ex-manufacturer price; met = metastatic; q4w = every 4 weeks; RSA = risk sharing arrangement; ToT = time on treatment.
1 Year-1 price
2 pro rata price per 4 weeks, based on the standard dose of 200 mg q3w

4 Scope of the proposed listing

4.1 The proposed listing includes all current and future TGA indications in the advanced/metastatic setting:

- 11 indications with PBS subsidy
- 16 indications with TGA approval but no PBS subsidy
- 2 indications where TGA approval is expected later [redacted]

- mesothelioma, Merkel cell carcinoma

- 3 indications where TGA approval could occur [redacted]
  - Second line (2L) ovarian, first line (1L) dMMR-EC (single agent), UGI (± lenvatinib)

4.2 These indications are summarised by PBS subsidy and TGA approval in Table 3 and Table 4.

4.3 The proposed listing does not include early-stage cancers nor rare cancers or off-label uses.

4.4 The September 2024 submission included a separate Authority Required item-code for ultra-rare tissue types that are not dMMR/MSI-H nor TMB-H. The current proposal does not include these tissue types. The submission notes the sponsor received feedback from clinicians that non-clear cell RCC (KN-B61), non-CRC dMMR and MSI-H tumours (KN-158), TMB-H tumours (KN-158), and HER2+ Gastric cancer (KN-811) as the most significant access gaps and there was minimal support for an unrestricted listing that could result in significant use outside the registered indications.

Table 3: Current and anticipated pembrolizumab indications by PBS-subsidy status and TGA-approval status

Registered and PBS Listed	Registered but not PBS listed	Not registered
Melanoma	cSCC	Merkel cell carcinoma
NSCLC	RCC (all risk strata) clear and non-clear cell	Mesothelioma
RCC (poor/intermediate) clear cell	UC (+EV)	EC (1L single-agent) dMMR
UC 2L	EC (1L with/after chemo) (dMMR agnostic)	Ovarian 2L
EC (2L with lenvatinib) (dMMR agnostic)	Upper GI GOJC, GC (HER2-neg and HER2-pos) OSCC, OAC	Upper GI GC (+ len) OSCC (+len) OSCC LA
CxC (metastatic and locally advanced with/after chemo-rads)	BTC	
CRC (dMMR/MSI-H)	Pan-tissue dMMR/MSI-H	
SCCHN	Pan-tissue TMB-H	
TNBC		
cHL R/R		
PMBCL R/R		

BTC = biliary tract carcinoma; cHL = classical Hodgkin's lymphoma; CRC = colorectal cancer; cSCC = cutaneous squamous cell carcinoma; dMMR = mismatch repair deficient; CxC =cervical cancer; EC = endometrial carcinoma; EV = enfortumab vedotin; GC = gastric cancer; GI = gastrointestinal; GOJC = gastro-oesophageal adenocarcinoma; HER2-neg = human epidermal growth factor receptor 2-negative; HER2-pos = human epidermal growth factor receptor 2-positive; LA = locally advanced; MSI-H = microsatelline instability-high; NSCLC = non-small cell lung cancer; OAC = oesophageal adenocarcinoma; OSCC = oral squamous cell carcinoma; PMBCL = primary mediastinal B-cell lymphoma; PBS = Pharmaceutical Benefits Scheme; RCC = renal cell carcinoma; R/R = relapsed or refractory; SCCN = squamous cell carcinoma of the head and neck; TGA = Therapeutic Goods Administration; TMB-H = tumour mutational burden-high; TNBC = triple negative breast cancer; UC = urothelial cancer; 1L – first line; 2L = second line.

Table 4: Indications included in the proposal

Tier	Trial ID	Indication	TGA Approval	PBS Listed[1]
Tier 1: Indications currently PBS listed (metastatic and advanced only)	KN189, KN407, KN042, KN024	NSCLC, Stage IV	Approved	Listed
	KN006	Melanoma, advanced	Approved	Listed
	KN045	UC	Approved	Listed
	KN087, KN204	cHL	Approved	Listed
	KN355	TNBC, metastatic	Approved	Listed
	KN048	HNSCC, metastatic	Approved	Listed
	KN826	Cervical, metastatic	Approved	Listed
	KN177	CRC	Approved	Listed
	KN170	PMBCL	Approved	Listed
	KN775	Endometrial, 2L	Approved	Listed
	KN581	RCC, metastatic	Approved	Listed
Tier 2a: Future indications where there is no PD-(L)1 available				
	KN052	Platinum ineligible UC	Approved	Jan-26
	KN158	TMB-H pan tumour	Approved	Jan-26
	KN164/KN158	MSI-H pan tumour	Approved	Jan-26
	KN581 (Fav risk)	RCC, favourable risk	Approved	Jan-26
	KNB61	RCC, non-clear cell	Approved	Jan-26
	KN811	Gastric, HER2+	Approved	Jan-26
	KNA39	1L UC EV + pem	Approved	Feb-26
Tier 2b: Future indications where a PD-(L)1 is available on PBS	KN590	Oesophageal, metastatic	Approved	Jan-26
	KN859	Gastric, HER2-	Approved	Jan-26
	KN629	cSCC	Approved	Jan-26
	KN483	Mesothelioma		
	KN966	Biliary	Approved	Jan-26
	KN913	1L Merkel Cell Carcinoma		
	KN868 (dMMR)	dMMR 1L Endo	Approved	Jan-26
	KN868 (pMMR)[2]	pMMR 1L Endo	Approved	Jan-26
	LEAP-014	Oesophageal, Pem + Len		
	KN426[3]	RCC, metastatic, Pem + Axi	Approved	Jan-26
	KNC93[3]	Endometrial (dMMR), Mono		
	KN040[3]	2L H&N	Approved	Jan-26
	KN010[3]	2L NSCLC	Approved	Jan-26

Axi = axitinib; cHL = classical Hodgkin's lymphoma; CRC = colorectal cancer; cSCC = cutaneous squamous cell carcinoma; dMMR = mismatch repair deficient; EV = enfortumab vedotin; HER2 = human epidermal growth factor receptor 2; HNSCC = head and neck squamous cell cancer; H&N = head and neck Len = lenvatinib NSCLC = non-small cell lung cancer; pem = pembrolizumab; PMBCL = primary mediastinal B-cell lymphoma; PBS = Pharmaceutical Benefits Scheme; RCC = renal cell carcinoma; TGA = Therapeutic Goods Administration; TNBC = triple negative breast cancer; UC = urothelial cancer; 1L – first line; 2L = second line.

[1] Assumes expanded listing to pembrolizumab is effective 1 Jan 2026

[2] Included in Tier 2b given the near-term comparators of Durva (PBAC approved Nov 2024) and Dosta (pending May 2025 PBAC meeting)

[3] No volume or value has been allocated to these indications, given the very small predicted uptake. Included for completeness, as these indications will be listed in the TGA PI

5 Requested Listing

5.1 The Secretariat has provided proposed amendments to the proposed restrictions with deletions as strikethrough and additions in italics.

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	№.of Rpts
PEMBROLIZUMAB Injection	*NEW (Public) NEW (Private)*	*400 mg*	*7*
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 Hospitals **Prescriber type:** ☒ Medical Practitioners **Restriction Type:** Authority Required – Streamlined			
Indication: Advanced and metastatic cancers			
Clinical Criteria:			
The treatment must be for an indication as specified in the TGA-approved PI			
Treatment Criteria:			
Patient must be undergoing treatment with this drug administered once every 3 weeks - prescribe up to 7 repeat prescriptions;			
Patient must be undergoing treatment with this drug administered once every 6 weeks - prescribe up to 3 repeat prescriptions			
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*			
~~**Population criteria:**~~			

~~Use must be in one of the indications described below:~~

~~Melanoma~~

- ~~monotherapy for the treatment of unresectable or metastatic melanoma in adults.~~

~~Non-small cell lung cancer (NSCLC)~~

- ~~in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumour aberrations.~~
- ~~in combination with carboplatin and either paclitaxel or nabpaclitaxel, for the first-line treatment of patients with metastatic squamous NSCLC.~~
- ~~monotherapy for the first-line treatment of patients with NSCLC expressing PD-L1 [tumour proportion score (TPS) ≥1%] as determined 1 by a validated test, with no EGFR or ALK genomic tumour aberrations, and is stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic.~~
- ~~monotherapy for the treatment of patients with advanced NSCLC whose tumours express PD-L1 with a ≥1% TPS as determined by a validated test and who have received platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received prior therapy for these aberrations prior to receiving treatment.~~

~~Head and Neck Squamous Cell Cancer (HNSCC)~~[1]

- ~~as monotherapy for the first-line treatment of patients with metastatic or unresectable recurrent HNSCC, and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥20] as determined by a validated test OR in combination with platinum and 5fluorouracil (5-FU) chemotherapy, for the first-line treatment of patients with metastatic or unresectable recurrent HNSCC~~
- ~~monotherapy for the treatment of patients with metastatic or unresectable recurrent HNSCC with disease progression on or after platinum containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥20] as determined by a validated test.~~

~~Classical Hodgkin Lymphoma (cHL)~~

- ~~monotherapy for the treatment of adult and paediatric patients with relapsed or refractory classical Hodgkin Lymphoma (cHL): 1. following autologous stem cell transplant (ASCT) or 2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.~~

~~Primary mediastinal B-Cell Lymphoma (PMBCL)~~

- ~~adult and paediatric patients with refractory primary mediastinal B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy.~~

~~Urothelial carcinoma~~

- ~~in combination with enfortumab vedotin, is indicated for the first-line treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC).~~
- ~~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.~~

~~Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) Cancer~~

- ~~adult and paediatric patients with unresectable or metastatic solid tumours that are MSI-H or dMMR, as determined by a validated test, that have progressed following prior treatment and when there are no satisfactory alternative treatment options.~~

~~Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) Colorectal Cancer~~

- ~~patients with unresectable or metastatic colorectal cancer (CRC) that is MSI-H or dMMR as determined by a validated test.~~

~~Biliary Tract Carcinoma~~

- ~~in combination with gemcitabine and cisplatin, for the treatment of patients with locally advanced unresectable or metastatic biliary tract carcinoma (BTC).~~

~~Endometrial carcinoma~~ [2]

- in combination with carboplatin and paclitaxel, followed by pembrolizumab as a single agent, it is indicated for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma.
- in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Cervical Cancer [3]

- in combination with platinum chemotherapy and paclitaxel, with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of patients with advanced renal cell carcinoma (RCC).
- in combination with lenvatinib for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

Cutaneous Squamous Cell Carcinoma

- monotherapy for the treatment of adult patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation

Gastric Cancer

- in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction (GOJ) adenocarcinoma that is not HER2-positive.
- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GOJ) adenocarcinoma, whose tumours express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

Oesophageal Cancer

- in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced or metastatic carcinoma of the oesophagus or HER2-negative gastroesophageal junction (GOJ) adenocarcinoma (tumour centre 1 to 5 centimetres above the GOJ) that is not amenable to surgical resection or definitive chemoradiation.

Tumour Mutational Burden-High (TMB-H) cancer

- adult and paediatric patients with unresectable or metastatic tumour mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Triple-Negative Breast Cancer

- in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 (CPS ≥10) as determined by a validated test and who have not received prior chemotherapy for metastatic disease.

[1] The TGA indication for HNSCC is restricted to patients with PD-L1 expressing tumours and a CPS ≥1 for both monotherapy and platinum-based chemotherapy. However, this restriction has been updated to reflect the current PBS restriction which permits treatment for patients with CPS ≥20 for monotherapy and for all patients when combined with platinum-based chemotherapy.
[2] The TGA indication for advanced endometrial carcinoma is limited to patients without MSI-H or dMMR. However, this restriction has been updated to reflect the current PBS restriction which permits treatment regardless of biomarker status for both pMMR and dMMR patients.
[3] The TGA indication for cervical cancer is confined to the PD-L1 ≥1% cohort. However, this restriction has been updated to reflect the current PBS restriction which allows treatment in all patients.

5.2 The submission proposed a single item-code (duplicated for the private and public hospital settings) that specifies each advanced and metastatic indication for which Keytruda® is registered for in the Australian Register of Therapeutic Goods (ARTG).

5.3 The wording of the proposed restrictions was drawn from the wording of the ARTG registration for the majority of indications. The following existing listings were intended to retain their current wording to ensure continued patient access for the existing PBS population:

- HNSCC
    - TGA: CPS ≥1 for both monotherapy and platinum-based chemotherapy.
    - PBS: CPS ≥20 for monotherapy; CPS agnostic in combination with platinum-based chemotherapy.
- 2L EC (+ lenvatinib)
    - TGA: patients without MSI-H or dMMR
    - PBS: agnostic to dMMR/pMMR status
- cervical cancer
    - TGA: PD-L1 ≥ 1%
    - PBS: agnostic to PD-L1 status.

5.4 The following is from the submission on the approach of aligning the wording of the PBS restrictions to TGA-approved indications. "... this alignment is a crucial aspect of this restriction ... there are significant Quality Use of Medicines risks associated with a PBS listing not linked to TGA indications. Additionally, without TGA links, PD-(L)1 inhibitors could be used interchangeably, which is inappropriate due to the important molecular differences and varying levels of clinical trial evidence among them."

5.5 The proposed approach would require an update to the restriction to align with any future changes to the relevant registered indications for pembrolizumab. There is no mechanism to support automatic updating of PBS restrictions when changes to the registration are made. As such, the proposed approach would require manual review or monitoring of the PI; notification by the sponsor or another party to the Department; and actions to implement any updated indications.

5.6 The proposed approach would allow for retreatment as this is not explicitly excluded by the product's registered indications.

5.7 The submission proposed to remove restriction criteria limiting treatment to a maximum of 24-months. The submission noted clinician feedback raised that providing this greater flexibility may allow treatment to be stopped earlier in some instances, especially in those patients who achieve a complete response, knowing that they can later retreat upon progression/recurrence if needed. One clinician highlighted that the cost of retreatment in the subset of patients who experience recurrence would be partially offset by shorter time on treatment for some complete responders who may have otherwise been maintained on therapy for the full 35 cycle / 24month duration. The current 24-month limit for time on treatment is driven by the pivotal registration studies.

5.8 The pre-PBAC response acknowledged extending time on treatment would be outside the current scope of the product registration but that this had been included due to the strong support for this change from the clinical community and that the sponsor considered this was a less significant quality use of medicine risk compared to a listing for indications not registered by the TGA. The pre-PBAC response noted the sponsor had provided information that would allow the committee to consider the impacts of including or removing this criterion.

5.9 The proposed approach of including all relevant wording from the TGA registration would mean multiple clinical restriction criteria or prescribing instructions would be required for many indications, making the listing overly long and complicated. The Secretariat proposed the listing could instead include the following clinical criterion:

Clinical Criteria:
The treatment must be for an indication as specified in the TGA-approved PI.

5.10 However, the above clinical criteria would not account for the additional indications specified in paragraph 5.3.

5.11 The pre—PBAC response argued the importance of maintaining a more complex listing to ensure appropriate use of the listing. It cited four primary concerns:

- an increased risk of leakage into settings that were not intended to comprise part of this proposal;
- more restrictive access for some cancer types compared with the PBS restrictions today (which the sponsor argued its proposal addressed more appropriately);
- an ability to control the timing of the inclusion of indications where pembrolizumab is used in combination with a high-cost agent; and
- concerns that it may be administratively burdensome for clinicians to require review of the TGA PI when considering the PBS restriction wording.

5.12 The submission did not specify the requested maximum amount or repeats. The Secretariat proposed 400 mg and 7 repeats, which is the largest amount and number of repeats currently available for a pembrolizumab listing.

5.13 The Secretariat proposed the inclusion of the following treatment criteria to align with existing listings, with the intention of providing approximately 6 months of treatment per prescription:

Treatment Criteria:
Patient must be undergoing treatment with this drug administered once every 3 weeks - prescribe up to 7 repeat prescriptions;
Patient must be undergoing treatment with this drug administered once every 6 weeks - prescribe up to 3 repeat prescriptions.

5.14 The submission stated flow-on changes to the PBS restrictions for lenvatinib may be required in the context of a broad listing for pembrolizumab. Three of the 20 new indications are used in combination with lenvatinib (non-clear cell RCC, favourable risk RCC, 1L oesophageal). The Secretariat reviewed the affected listings, which included a reference to use in combination with pembrolizumab. As these requirements could still be met under a broad listing of pembrolizumab, the implementation of a broad listing would not require flow on changes to lenvatinib.

5.15 The submission noted all but one existing advanced or metastatic listing is an Authority Required (Streamlined) listing; dMMR colorectal cancer is an authority required listing. The submission stated the PBAC had considered this Authority type to be appropriate at the time of recommending supporting MMR testing eligibility requirements were met. The submission noted the listing had been in place since 2021 and stated the lack of efficacy of immunotherapy as monotherapy in pMMR is well established. It therefore considered it would be appropriate, in the context of a broad

listing, for dMMR colorectal cancer to also be included in the proposed Authority Required (Streamlined) listing and that this would be consistent with the existing PBS listing of dostarlimab in dMMR endometrial cancer.

Testing for MSI-H and TMB

5.16 dMMR can be reasonably accurately detected via immune histochemistry (IHC) testing and there is an MBS item for IHC that covers all tissue types. IHC is sufficient in most cases, but in a few cases MSI genomic testing is required.

5.17 TMB is different: genomic testing is needed, for which there is currently no MBS item. Patients would have to access TMB testing via referral to the CaSP program operated by Omico, case by case public hospital funding, or private funding.

6 Proposed Pricing

Overview

6.1 The submission proposed that lower prices for the broader additional indications and treatment settings are achieved through a price-volume agreement (PVA).

6.2 No upfront reduction to the current pembrolizumab price was proposed. The submission proposed to maintain the current effective prices through implementing a single, weighted, effective price (AEMP) for pembrolizumab 100 mg of $[redacted] ($[redacted] q4w). The weighted price considered by PBAC in December 2023 (pre-PBAC) was ~$[redacted] per 100 mg ($[redacted] q4w).

6.3 Correcting the melanoma price and using the submission's methodology reduces the weighted price to $[redacted] per 100 mg.

6.4 A weighted price is required as the proposed PBS restriction would require a single multi-indication PBS item, covering existing and new/additional unresectable advanced or metastatic indications.

6.5 The proposed weightings were based on the 6-year forecast script volumes for each advanced/metastatic indication currently PBS listed.

6.6 Price discounts were proposed for additional indications (Tier 2), additional use (Tier 3) and a fourth tier referred to as a 'risk-share allowance' (Tier 4). The submission stated that discounts account for the use being expected to be less cost-effective than use in currently listed PBS indications (Tier 1).

- Tier 1: based on weighted price for existing indications
- Tier 2: [redacted]% price reduction from Tier 1 for additional TGA indications
- Tier 3: [redacted]% price reduction from Tier 1 for uses in retreatment and extended time on treatment (i.e. beyond 24 months)
- Tier 4: [redacted]% price reduction from Tier 1 for utilisation [redacted]% above Tier 3.

The submission suggested that a [redacted]% rebate would apply at some level higher than Tier 4, but did not provide any further details of the proposed basis for this cap .

6.7 The Pre-PBAC response confirmed that a [redacted]% rebate would apply as a 'Tier 5' for utilisation beyond Tier 4.

Table 5: Proposed effective AEMP per 100 mg vial for each tier

Tier	Price (AEMP)	% Discount v Tier 1
1	$[redacted]	[redacted]%
2	$[redacted]	-[redacted]%
3	$[redacted]	-[redacted]%
4	*$[redacted]	-[redacted]%
5	$[redacted]	-[redacted]%

AEMP = approved ex-manufacturer price
*Sponsor was asked to confirm this price in its pre-PBAC response – see Table 2

6.8 If the forecast utilisation is not reached, then the price discounts would not be achieved.

6.9 The proposed weightings per indication and resultant effective price for pembrolizumab are provided in Table 6.

Table 6: Pembrolizumab effective price per vial (AEMP) for existing PBS listed indications for advanced and metastatic cancers

Indication	Price per vial (AEMP)	Price per 100 mg (corrected by Dept)
NSCLC, Stage IV	$[redacted]	$[redacted]
Melanoma, advanced	$[redacted]	$[redacted]
UC	$[redacted]	$[redacted]
cHL	$[redacted]	$[redacted]
TNBC, metastatic	$[redacted]	$[redacted]
HNSCC, metastatic	$[redacted]	$[redacted]
Cervical, metastatic	$[redacted]	$[redacted]
CRC	$[redacted]	$[redacted]
PMBCL	$[redacted]	$[redacted]
Endometrial, 2L	$[redacted]	$[redacted]
RCC, metastatic	$[redacted]	$[redacted]

AEMP = approved ex-manufacturer price; cHL = classical Hodgkin's lymphoma; CRC = colorectal cancer; Dept = Department; HNSCC = head and neck squamous cell carcinoma; NSCLC = non-small cell lung cancer; PMBCL = primary mediastinal B-cell lymphoma; PBS = Pharmaceutical Benefits Scheme; RCC = renal cell carcinoma; TNBC = triple negative breast cancer; UC = urothelial cancer; 2L = second line.

Table 7: Proportion of Tier 1 utilisation by indication

Indication	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
NSCLC, Stage IV	52%	54%	57%	59%	59%	59%
Melanoma, advanced	11%	11%	11%	11%	11%	11%
UC	1%	1%	0%	0%	0%	0%
cHL	2%	2%	2%	2%	2%	2%
TNBC, metastatic	3%	3%	3%	2%	2%	2%
HNSCC, metastatic	8%	9%	9%	8%	8%	8%
Cervical, metastatic	5%	5%	5%	5%	5%	5%
CRC	6%	5%	4%	4%	4%	4%
PMBCL	0%	0%	0%	0%	0%	0%
Endometrial, 2L	4%	3%	2%	1%	1%	1%
RCC, metastatic	7%	7%	7%	7%	7%	7%
	100%	100%	100%	100%	100%	100%
Weighted average price per year	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

cHL = classical Hodgkin's lymphoma; CRC = colorectal cancer; HNSCC = head and neck squamous cell carcinoma; NSCLC = non-small cell lung cancer; PMBCL = primary mediastinal B-cell lymphoma; RCC = renal cell carcinoma; TNBC = triple negative breast cancer; UC = urothelial cancer; 2L = second line.

6.10 The relative percentage of NSCLC scripts might not increase over time as modelled due to an increasing uptake of peri-operative immune-therapy and the expectation that an increasing number of patients will be cured and not have (advanced) local or metastatic recurrence.

6.11 The increasing uptake of peri-operative immune-therapy for other tissue types may reduce usage in the advanced/metastatic setting over the forward estimates.

6.12 The relative percentage of dMMR CRC scripts might reduce further than predicted with the introduction of other immune therapies into the market.

6.13 The relative percentage of R/R cHL scripts might reduce over time if immune-therapy is used in newly diagnosed patients as per current guidelines.

Tier 2 (existing and expected TGA indications that are not currently PBS listed)

Table 8: Modelled effective prices for future advanced and metastatic cancer indications

Indication	Price per vial (AEMP)	Pricing rationale
Ovarian, metastatic	$[redacted]	Assumes price parity with mTNBC which is a similar cancer type (difficult-to-treat women's cancer)
Platinum ineligible UC	$[redacted]	Assumes parity with adj RCC
TMB-H pan tumour	$[redacted]	dMMR CRC price [redacted] / variation across tumours
MSI-H pan tumour	$[redacted]	dMMR CRC price [redacted] / variation across tumours
RCC, favourable risk	$[redacted]	Sunitinib price (estimated)
RCC, non-clear cell	$[redacted]	Same price as 1L ccRCC price on the basis that incremental benefit over TKI monotherapy is likely to be the same in nccRCC as ccRCC
Gastric, HER2+	$[redacted]	Assumes parity with HER2- Gastric
Oesophageal, metastatic	$[redacted]	Nivolumab price
Gastric, HER2-	$[redacted]	Nivolumab price
cSCC	$[redacted]	Cemiplimab price
Mesothelioma	$[redacted]	Nivolumab price (estimated)
Biliary	$[redacted]	Durvalumab price (estimated)
1L Merkel Cell Carcinoma	$[redacted]	Avelumab price (estimated)
dMMR 1L Endo	$[redacted]	Dostarlimab price (estimated)
pMMR 1L Endo	$[redacted]	Dostarlimab price (estimated)
1L UC EV + pem	$[redacted]	Placeholder price - will be updated [redacted]
Oesophageal, Pem + Len	$[redacted]	Nivolumab price
RCC, metastatic, Pem + Axi	$0.00	N/A - no volume has been associated with this indication
Endometrial (dMMR), Mono	$0.00	N/A - no volume has been associated with this indication
2L H&N	$0.00	N/A - no volume has been associated with this indication
2L NSCLC	$0.00	N/A - no volume has been associated with this indication

adj = adjuvant; AEMP = approved ex-manufacturer price; Axi = axitinib; ccRCC = clear cell renal cell carcinoma; CRC = colorectal cancer; cSCC = cutaneous squamous cell carcinoma; dMMR = mismatch repair deficient; EV = enfortumab vedotin; HER2 = human epidermal growth factor receptor 2; H&N = head and neck; Len = lenvatinib microsatellite instability-high (MSI-H); mTNBC = metastatic triple negative breast cancer; nccRCC = non clear cell renal cell carcinoma; NSCLC = non-small cell lung cancer; pem = pembrolizumab; RCC = renal cell carcinoma; TMB-H = tumour mutational burden-high; UC = urothelial cancer; 1L – first line; 2L = second line.
Blue cells indicate a price already established through PBAC process and price is known to MSD (i.e. pembrolizumab has been recommended on a cost-minimisation basis)
Purple cells indicate prices that have been established through the PBAC process but are not known by MSD
White cell indicates a proxy price proposed by MSD where no PBS price is established

6.14 The proposed weighted price for Tier 2 across 6 years is $[redacted] per 100 mg or $[redacted] Q4W. This is a [redacted]% discount on the Tier-1 weighted price.

6.15 The submission stated the weighted price could change depending on:

- uptake for indications where there is already a PD-(L)1 inhibitor listed; e.g., cSCC, EC, UGI, OSCC, BT, mesothelioma, Merkel cell carcinoma. The PBAC noted there is considerable uncertainty in these estimates.

- the effective price of comparators not known to the sponsor (e.g., dostarlimab/durvalumab in dMMR EC, durvalumab in BT, nivolumab in mesothelioma)
- whether the sponsor of a partner/combination medicine decides to list (e.g., enfortumab vedotin, lenvatinib).

6.16 The submission also stated the 'majority of pembrolizumab's future metastatic indications are already TGA approved. Of the 20 new indications that are contained within this proposal, 15 are already TGA-approved and three others have met their primary endpoint', which it claimed provided additional support to the certainty of the estimates of the future use of pembrolizumab.

6.17 The sponsor was asked to justify why indications that have a positive PBAC recommendation and not yet implemented would not be included in the calculation of the baseline price used for Tier 1 (where cost-effectiveness has been assessed). The pre-PBAC response argued that including these indications in Tier 1 would reduce the certainty in the uptake of Tier 1 due to the immaturity of the listings compared to those proposed for inclusion in Tier 1 which have been listed for 2 or more years. The pre-PBAC response also noted this would reduce the weighted price and require the sponsor to seek updated pricing approval.

Tier 3 (retreatment and use beyond 24 months)

6.18 The submission proposed a [redacted]% price discount for utilisation above Tier 2 which is intended to account for utilisation in retreatment and extended time on treatment scenarios. The submission acknowledges this discount is intended to account for the expectation that efficacy would be lower in these settings.

6.19 Refer to paragraphs 8.7 and 8.8 for comments about the uncertainty in relation to the utilisation estimates informing the Tier 3 caps.

Tier 4

6.20 The submission proposed the inclusion of a 'risk share allowance' (Tier 4) for utilisation [redacted]% above Tier 3. The cost of pembrolizumab would be provided at a further discounted price ([redacted]% of the Tier 1) before reaching any subsidisation cap, with a 100% rebate. Further information is outlined in the Risk Sharing Arrangement section.

6.21 The submission stated this would represent good value-for-money as, should pembrolizumab use increase due to higher brand share in Tiers 1 or 2, due to simplifying prescribing, or if future competitors or early-stage listings do not proceed, this cost-effective use of pembrolizumab will fall into Tier 4, where the price is further discounted.

7 Risk-sharing arrangement

Overview

7.1 The tiered subsidisation caps are presented below.

Table 9: Sponsor's proposed PBS/RPBS expenditure, multi-indication pembrolizumab listing*

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Tier 1	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Tier 2a	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Tier 2b	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Tier 3a	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Tier 3b	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

M = million; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
2a: additional pembrolizumab indications where there is no PD-(L)1i on the PBS
2b: additional pembrolizumab indications where a PD-(L)1i is available on the PBS
3a: retreatment
3b: use beyond 24 months
* Table accounts for expenditure on pembrolizumab only and does not incorporate Tier 4

Table 10: Total estimated PBS/RPBS expenditure for pembrolizumab under the broad listing

Tier	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Tiers 1-3	$[redacted][1]	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][3]
Tier 4	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][5]
Total	$[redacted][1]	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][3]

M = million; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
The redacted values correspond to the following ranges:
[1] *$200 million to < $300 million*
[2] *$300 million to < $400 million*
[3] *> $1 billion*
[4] *$10 million to < $20 million*
[5] *$80 million to < $90 million*

7.2 The submission's forecasts for Tier-1 (current listings) vary from between $100 million to < $200 million and $100 million to < $200 million per year.

7.3 The forecasts for the additional indications (Tier 2, Tier 3, Tier 4) vary from approximately $40 million to < $50 million in Year 1 to $100 million to < $200 million in Year 6.

7.4 Under the submission's proposal, maintaining cost-effectiveness is reliant on the accuracy of the estimates which both the sponsor and Secretariat noted are subject to considerable uncertainty. Using multiple tiers increases this reliance on the estimates to achieve cost-effectiveness across the different treatment settings. A simpler approach with an upfront price reduction or RSA approach with a single weighted discount applied after Tier 1 and an overall cap on expenditure is likely to reduce uncertainty in managing the overall financial impact and ensuring use occurs at the appropriate price in each treatment setting.

7.5 The Drug Utilisation Section reviewed the provided model and estimates used to inform the proposed pricing and RSA. For further information on this review, see Section 8.

Tier 1: existing PBS-listed indications

7.6 For Tier 1 indications, details of the forecasts have not been provided. The sponsor stated in the submission that this is because the PBAC has already reviewed and accepted the utilisation estimates. Refer to Table 15 below for a comparison of the sponsor's estimates compared to forecasts based on the agreed financial estimates.

7.7 The submission stated that the estimates take into account the impact of anticipated PBS listings, both in the same indication and in earlier lines of therapy given the potential impact on incident patient numbers in late-stage disease.

Tier 2: extended indications

7.8 Tier 2 indications have been categorised into one of two subcategories based on whether the PBAC has previously reviewed utilisation estimates for another PD-(L)1 inhibitor in the same or similar population:

- Tier 2a: future indications where there is not a PD-(L)1i available on the PBS
- Tier 2b: future indications where a PD-(L)1i is available on the PBS.

Table 11: Sponsor's forecasts for additional pembrolizumab patients and scripts for indications where there is no PD-(L)1 inhibitor listed (Tier 2a)

New patients						
Indication[1]	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
2L ovary[1]						
1L UC cis ineligible[1]						
TMB-H pan-tissue[1]						
MSI-H pan-tissue[1]						
1L RCC low risk[1]						
1L RCC non clear cell[1]						
UGI HER2-pos[1]						
1L UC (+ EV)	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total[2]						
Scripts						
Indication	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
2L ovary[1]						
1L UC cis ineligible[1]						
TMB-H pan-tissue[1]						
MSI-H pan-tissue	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
1L RCC low risk	[redacted]	[redacted]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
1L RCC non clear cell	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
UGI HER2-pos	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
1L UC (+ EV)[2]						
Total[2]						
Scripts/patient						
Indication	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
2L ovary	1.8	6.8	15.7	12.8	12.0	11.4
1L UC cis ineligible	3.4	7.3	8.3	8.0	8.0	8.1
TMB-H pan-tissue	2.3	4.9	7.7	8.7	8.7	8.8
MSI-H pan-tissue	3.4	5.9	7.3	7.4	7.4	7.5
1L RCC low risk	5.4	11.2	15.7	17.0	17.2	17.5
1L RCC non clear cell	5.6	12.5	15.2	15.1	15.2	16.0
UGI HER2-pos	4.7	8.7	10.5	10.7	10.7	10.7
1L UC (+ EV)	3.7	7.5	10.2	10.6	10.5	10.7
Total	4.1	8.0	10.7	10.9	10.9	11.1

EV = Enfortumab vedotin; HER2-pos = human epidermal growth factor receptor 2-positive; MSI-H = microsatelline instability-high; RCC = renal cell carcinoma; TMB-H = tumour mutational burden-high; UC = urothelial cancer; UGI = upper gastro-intestinal; p1L = first line; 2L = second line

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 to < 5,000

7.9 There are the following uncertainties related to estimated script numbers in Table 11:

- ~ 60% of patients and scripts after Year-1 are forecast by the submission as due to 1L UC (+EV). Such uptake is plausible given efficacy of this combination. However, the start of the sharp uptake depends on when the listing is implemented following the PBAC recommendation in November 2024.
- ~ 10% of patients and scripts are forecast by the submission attributed to UGI HER2-positive cancer. Tislelizumab received a positive recommendation from PBAC at the November 2024 meeting for advanced/metastatic UGI cancers, including HER2-positive cancers; and was listed on the PBS on 1 April 2025. This may impact the forecast uptake in this indication.

- ~ <500 patients are forecast by the sponsor as due to cisplatin-ineligible UC. These are relatively small numbers, but may be overestimated. Nivolumab in combination with enfortumab vedotin was recommended for platinum-ineligible UC at the November 2024 PBAC meeting.

7.10 The forecast expenditure for Tier-2b (additional pembrolizumab indications where there is currently another PD-(L)1 inhibitor with a PBS listing) increases from approximately $10 million to < $20 million in Year 1 to $60 million to < $70 million by Year 6.

Table 12: Sponsor's forecasts for additional pembrolizumab patients and scripts for indications where there is another PD-(L)1 inhibitor listed (Tier 2b)

New patients						
Indication	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
1L OSCC[1]	[redacted]					
1L GOC HER2-neg[1]						
cSCC[1]						
Mesothelioma[1]						
BT[1]						
Merkel cell[1]						
1L dMMR EC[1]						
1L pMMR EC[1]						
1L OSCC (+ lenvatinib)[1]						
Total[2]						
Scripts						
Indication	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
1L OSCC[2]	[redacted]					
1L GOC HER2-neg[2]						
cSCC[2]						
mesothelioma	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
BT	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Merkel cell	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
1L dMMR EC[2]	[redacted]					
1L pMMR EC[2]						
1L OSCC (+ lenvatinib)[1]						
Total[2]						
Scripts/patient						
Indication	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
1L OSCC	4.4	7.0	7.4	8.3	9.7	9.9
1L GOC HER2-neg	3.8	6.8	7.8	7.8	7.7	7.7
cSCC	4.3	8.0	11.6	13.0	13.1	13.3
mesothelioma	4.4	7.5	8.6	8.6	8.4	8.3
BT	4.1	7.1	8.0	8.0	7.8	7.8
Merkel cell	5.2	10.3	13.2	13.4	12.7	12.0
1L dMMR EC	8.7	13.4	15.8	15.8	15.6	15.6
1L pMMR EC	8.7	14.1	16.5	16.6	16.4	16.4
1L OSCC (+ lenvatinib)	7.8	6.3	9.6	10.7	10.8	10.0
Total	4.4	7.0	7.4	8.3	9.7	9.9

BT = biliary tract; cSCC = cutaneous squamous cell carcinoma; dMMR = mismatch repair deficient; EC = endometrial carcinoma; GOC = gastro-oesophageal cancer; HER2-neg = human epidermal growth factor receptor 2-negative; OSCC = oral squamous cell carcinoma; 1L – first line.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

Table 13: Submission assumptions about pembrolizumab market share for indications where there is another PD-(L)1 inhibitor listed

Indication	Assumed market share versus other PD-(L)1 inhibitors
1L OSCC	[redacted]%
1L GOC HER2-neg	[redacted]%
cSCC	[redacted]%
mesothelioma	[redacted]%
BT	[redacted]%
Merkel cell	[redacted]%
1L dMMR EC	[redacted]%
1L pMMR EC	[redacted]%
1L OSCC (+ lenvatinib)	[redacted]%

BT = biliary tract cSCC = cutaneous squamous cell carcinoma; dMMR = mismatch repair deficient; EC = endometrial carcinoma; GOC = gastro-oesophageal; HER2-neg = human epidermal growth factor receptor 2-negative; OSCC = oral squamous cell carcinoma; 1L – first line.

7.11 There are uncertainties in the additional pembrolizumab scripts in Tier-2b which are due to assumptions about market share versus other PD-(L)1 inhibitors already listed on the PBS for the additional pembrolizumab indications. For example:

- 42% of the additional pembrolizumab scripts in Tier-2b are due to cSCC, based on the assumption that pembrolizumab will take [redacted]% of the cSCC market from cemiplimab.
- 10% of the additional pembrolizumab scripts in Tier-2b are due to 1L dMMR EC based on the assumption that pembrolizumab will take [redacted]% of the 1L dMMR EC market.
- 17% of the additional pembrolizumab scripts in Tier-2b are due to 1L pMMR EC based on the assumption that pembrolizumab will take [redacted]% of the 1L pMMR EC market, although a PD-(L)1 inhibitor is not currently listed on the PBS for 1L pMMR EC. An individual/separate submission for pembrolizumab in 1L dMMR and pMMR EC will be considered at the July 2025 PBAC meeting.

Tier 3: retreatment and extended time on treatment

7.12 The sponsor divided Tier 3 utilisation estimates into two groups:

- retreatment (Tier 3a)
- use beyond 24 months (Tier 3b).

7.13 The sponsor's forecast for Tier 3a (retreatment) increases from approximately $0 to < $10 million in Year 1 to $10 million to < $20 million in Year 6; the mean forecast is approximately $10 million to < $20 million per year.

7.14 The sponsor's forecast for Tier 3b (time-on-treatment longer than 24 months) increases from approximately $10 million to < $20 million in Year 1 to $20 million to < $30 million in Year 6; the mean forecast is approximately $20 million to < $30 million per year.

7.15 To account for the unknown efficacy and lack of randomised data in these patient groups, the submission proposed a [redacted]% price discount compared to the Tier 1 price (current indications) for utilisation above Tier 2 of the RSA.

7.16 The sponsor provided details of how the forecasts were estimated in sections 4.3 and 4.4 of the submission. The sponsor was asked to clarify how retreatment was dealt with in regard to the early setting to the metastatic setting or whether it also included retreatment from the 1L metastatic to the 2+L metastatic setting. The pre-PBAC response provided the following:

'Of the 32 indications included in the submission, 9 were in 2L+ populations. Of these indications, retreatment from 1L to 2L has been accounted for in 3: KN755 (Endometrial, 2L), KN158 (TMB-H pan tumour), and KN164/KN158 (MSI-H pan tumour). The remaining six indications in the 2L+ population did not account for retreatment due to several reasons, including the absence of listings in the earlier line, limited uptake of the indication, or the availability of treatments in both the early stage and 1L metastatic setting, making retreatment in 2L unlikely.'

7.17 The key uncertainties are:

- the number of patients who will be retreated and the mean number of scripts per patient in that setting
- whether use beyond 24 months should be included in the multi-indication proposal, given:
  - the forecast expenditure of $20 million to < $30 million per year.
  - the design of the pivotal RCTs, which limited treatment to 24 months (in many of the indications).
  - the dosing section of the TGA PI, which limits time-on-treatment to 24 months in line with the pivotal RCTs.

Tier 4: allowance

7.18 This proposed risk share allowance would be an incremental $[redacted] above Tier 3 in Year 1, increasing to $[redacted] in Year 6. See Table 14 for details.

Table 14: Pembrolizumab risk share allowance (Tier 4)

Tier	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Pembrolizumab - Tier 4	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

7.19 The PBAC noted that in creating a new cap arrangement for a broad listing, pembrolizumab would need to be removed from some existing shared RSAs (melanoma combined resected/unresectable; NSCLC; RCC; SCCHN; endometrial cancer).

8 Forecast PBS usage and financial implications

8.1 The utilisation estimates presented are based on the sponsor's internal commercial forecasts, which adopt an epidemiological approach. A high-level overview of the overarching principles and standard assumptions that were used for the commercial forecasts was provided in Section 4 'Forecasting assumptions' and Table 5 of the submission.

8.2 For the Tier 1 currently listed indications, the sponsor stated that future vials and scripts are projected based on current utilisation and these estimates consider the impact of anticipated PBS listings, both in the same indication and in earlier lines of

therapy given the potential impact on incident patient numbers in late-stage disease. However, no details were provided on the forecasting assumptions for these indications. Consequently, vial and script numbers could not be verified.

8.3 Table 15 presents comparisons of the submission forecasts for the Tier 2b indications versus the forecasts agreed by the Department of Finance at the time of listing and the actual number of patients supplied pembrolizumab in 2024. The agreed financial estimates are more consistent with the actual number of patients supplied PD-(L)1 in 2024 compared to the submission forecasts.

Table 15: Sponsor forecasts of future PBS listings for pembrolizumab compared to agreed financial estimates

	2024	2026	2027	2028	2029	2030	2031
PBS listed indication: Advanced or metastatic gastro-oesophageal cancers							
Submission estimated patient count[1]							
Department estimated patient count (at listing)[1]							
Department actual PBS/RPBS patients[1]							
PBS listed indication: Metastatic or locally advanced cutaneous squamous cell carcinoma							
Submission estimated patient count[1]							
Department estimated patient count (at listing)[1]							
Department actual PBS/RPBS patients[1]							
PBS listed indication: Unresectable malignant mesothelioma							
Submission estimated patient count[2]							
Department estimated patient count (at listing)[2]							
Department actual PBS/RPBS patients[1]							
PBS listed indication: Locally advanced, metastatic or recurrent biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer)							
Submission estimated patient count[2]							
Department estimated patient count (at listing)[1]							
Department actual PBS/RPBS patients[1]							
PBS listed indication: Stage IV (metastatic) Merkel Cell Carcinoma							
Submission estimated patient count[2]							
Department estimated patient count (at listing)[2]							
Department actual PBS/RPBS patients[2]							
PBS listed indication: Advanced, metastatic or recurrent endometrial carcinoma (dMMR)							
Submission estimated patient count[2]							
Department estimated patient count (at listing)[2]							
Department actual PBS/RPBS patients[2]							
PBS listed indication: Advanced, metastatic or recurrent endometrial carcinoma (pMMR)							
Submission estimated patient count[2]							
Department estimated patient count (at listing)[2]							
Department actual PBS/RPBS patients	Not yet implemented						

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] <500

8.4 For the Tier 2a future indications where there is no PD-(L)1i available, several of the overarching modelling assumptions and the output of patient and vial numbers from the sponsor's internal commercial forecasting model were provided. However, based on the level of detail that has been provided, the patient and vial numbers could not be verified.

8.5 For the Tier 2b future indications where a PD-(L)1i is available on the PBS, the projected number of new PD-(L)1i patients from the sponsor's internal forecasting model, along with the overarching assumptions on the pembrolizumab peak brand share, time to peak were provided. However, based on this information the patient and vial numbers could not be verified.

8.6 For the Tier 3a indications impacted due to the removal of once in a lifetime (OIAL) restriction, a general description of the steps to determine the number of newly recurrent patients from the sponsor's internal commercial forecasting model was provided along with several of the overarching modelling assumptions. However, based on this information the patient and vial numbers could not be verified.

8.7 For the Tier 3b indications impacted by the removal of the stopping rule (35 cycles/24 months), the sponsor provided details on the approach to determine the number of additional vials per patient per year for indications impacted by the removal of the stopping rule. The additional vials per patient per year were applied to the patient numbers from the sponsor's internal commercial forecast model. However, given that patient numbers and the methodology used to derive them could not be verified, the output of this approach could also not be verified.

8.8 The following elements need to be included in a future version of the model in order for the utilisation estimates to be suitable for consideration by the Department of Finance: details on the modelling methodology to enable verification of patient numbers, vials and scripts; inclusion of offset medicines for the Tier 2b indications; incorporation of patient copayments; impacts to Services Australia for increased service volumes for pembrolizumab and decreased volumes for affected medicines; appropriate impacts for the MBS, such as administration costs.

8.9 Table 16 provided in the submission estimated the net cost to the PBS/RPBS, including costs of therapies offset by pembrolizumab use, adding the cost of therapies administered in combination with pembrolizumab; and excluding the impact of patient co-payments (which it considered had a minimal impact on overall financial estimates).

Table 16: Net cost to PBS/RPBS including combination and displaced therapies

Tier	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Pembro Tier 1-3	$[redacted][1]	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][3]
Pembro Tier 4 (RSA)	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][5]
Total cost of add-ons	$[redacted][6]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][8]
Lenvatinib	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][7]
EV	$[redacted][10]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][11]
Trastuzumab	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][12]
Chemotherapy	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][9]
Changes to listings	-$[redacted][9]	-$[redacted][9]	-$[redacted][9]	-$[redacted][9]	-$[redacted][9]	-$[redacted][9]	-$[redacted][7]
Cabozantinib	-$[redacted][12]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][13]
Sac. govitecan	-$[redacted][12]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][6]
Chemotherapy	-$[redacted][12]	-$[redacted][12]	-$[redacted][12]	-$[redacted][12]	-$[redacted][12]	-$[redacted][12]	-$[redacted][4]
Net cost to PBS /RPBS	**$[redacted][1]**	**$[redacted][14]**	**$[redacted][14]**	**$[redacted][14]**	**$[redacted][14]**	**$[redacted][14]**	**$[redacted][3]**

Source: Table 68, p67 of submission

EV = enfortumab vedotin Sac. govitecan = sacituzumab govitecan; Pembro: pembrolizumab; RSA = risk sharing arrangement

The redacted values correspond to the following ranges:

[1] *$200 million to < $300 million*

[2] *$300 million to < $400 million*

[3] *> $1 billion*

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

[5] *$80 million to < $90 million*

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

[7] *$100 million to < $200 million*

[8] *$800 million to < $900 million*

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

[10] *$50 million to < $60 million*

[11] *$600 million to < $700 million*

[12] *$0 to < $10 million*

[13] *$70 million to < $80 million*

[14] *$400 million to < $500 million*

9 Additional Considerations

Sponsor hearing

9.1 There was no hearing for this item.

Consumer comments

9.2 The PBAC noted and welcomed the input from health care professionals (7), and clinical organisations (4) and consumer representatives organisations (2). The PBAC noted input from medical oncologists and the clinical groups were broadly supportive of an expanded listing of pembrolizumab, particularly where there is evidence of benefit in the advanced/metastatic setting and use was in line with TGA registered indications. Consumer organisations noted the significant financial burden associated with treatment and the perceived inequity of access across the existing PBS listed indications. Input highlighted the benefits of broader access for individuals with rare, advanced cancers. Several inputs highlighted the benefits of allowing access to retreatment and extended time on treatment for patients where this is clinically appropriate. Some input noted the importance of ensuring that utilisation occurred only in conditions for which there was evidence of efficacy and it would be important to safeguard against inappropriate use or risk in indications where there is no evidence of benefit.

10 PBAC Outcome

10.1 The PBAC did not recommend a multi-indication (broad) listing for pembrolizumab in advanced or metastatic cancers. In providing this advice, the PBAC considered the proposal for the broad listing did not establish a reliable basis for the financial estimates, which also raised significant uncertainty in the ability to achieve a cost-effective listing, given the complex pricing and Risk Sharing Arrangement (RSA) structure proposed.

10.2 The PBAC noted the proposal was restricted to the TGA registered indications for pembrolizumab and, as such, would not provide access to some of the groups in which there is a significant unmet clinical need, such as rare cancers. The PBAC noted a regulatory and subsequent submission for subsidy was unlikely to be made for these patient groups with rare cancers, and recalled it was access for this area of clinical need that was one of the initial driving factors behind the broad listing proposals for PD-(L)1 inhibitors.

10.3 The PBAC noted the sponsor had previously indicated it considered a separate arrangement for rare cancers would be required. However, the PBAC considered it would be important that a proposal with a separate arrangement addressing this patient group be brought forward either as part of, or in parallel with, the broad listing proposal.

10.4 The PBAC acknowledged that the standard utilisation and cost model template had not been used as part of the submission due to the complexity of the proposal which spanned multiple indications and treatment scenarios. The PBAC noted that the non-standard model was discussed with the Department prior to its submission. However, the PBAC considered the model provided did not provide sufficient clarity as to the inputs and underlying assumptions driving the outputs and that this difficulty in verifying the outputs of the financial model meant it was not reliable for decision making. The PBAC noted this also diminished the PBAC's ability to provide advice on what it considered would be appropriate amendments to the model and its underlying assumptions to support any future submission. The PBAC noted that the department was not able to validate the presented estimates, in particular the inclusion of formulas to facilitate replicating the calculation of the outputs.

10.5 The PBAC noted that further work would be required between the sponsor and the Department to agree on an approach to the restrictions that was implementable. The PBAC was not opposed to the sponsor's approach provided it could be reasonably implemented and interpreted by prescribers.

10.6 The PBAC noted under the sponsor's proposed approach to the restrictions that a mechanism to update the listing with future regulatory changes would be required. The PBAC noted the pre-PBAC response had indicated only a small number of future regulatory updates were anticipated in the advanced and metastatic cancer stage. The PBAC considered this issue should be addressed in any future proposals and that the sponsor may wish to engage with the Department in the development of how that mechanism to update the listing would be operationalised.

Pricing

10.7 The PBAC noted a single weighted price was proposed for the existing advanced/metastatic indications currently PBS listed based on forecast volumes. The

PBAC considered use of a weighted price to maintain the price of existing indications was an acceptable approach.

10.8 The PBAC noted this weighted price was proposed to be applied to utilisation under the first tier of the proposed RSA and the cap for utilisation would be set based on extrapolated utilisation of the existing listings. This was intended to effectively maintain the existing prices for current listings.

10.9 The PBAC reaffirmed its view that a cap on overall expenditure would be appropriate given the level of uncertainty in uptake and potential for leakage outside the intended populations.

10.10 The PBAC noted the price discount offered between Tier 1 and Tier 2 in the submission resulted in a price that was higher than the price for some existing PBS listed advanced/metastatic indications. The discount was increased in the pre-PBAC response, however the PBAC considered it was insufficient to ensure the treatment would be cost-effective in these extended indications where cost-effectiveness is likely to be lower on average compared to existing indications. The PBAC also noted that there were indications included in Tier 2, including gastro-oesophageal cancer and cSCC, where cost-effectiveness had already been evaluated and were better accounted for in the base (Tier 1) price. The indicative prices for these indications were lower than the proposed price for Tier 2. The PBAC considered a more substantive price reduction for use beyond existing listed or recommended advanced/metastatic indications (Tier 1) would be required.

10.11 The PBAC considered a further reduction for use in retreatment and extended time on treatment would be required to ensure those uses were cost-effective.

Risk Sharing Arrangement

10.12 The PBAC noted the sponsor initially proposed a five-tier RSA with increasing discounts to reflect different circumstances of use. The PBAC noted that cost-effectiveness of the listing would be heavily reliant on the estimates used to inform each tier to ensure the price reductions would be achieved.

10.13 The PBAC considered, given the inherent uncertainty associated with estimating utilisation under the proposal, that the risk of not achieving the intended price reductions was increased with each additional tier of the RSA. The PBAC advised that a simplified RSA structure with a consolidated discount beyond Tier 1 would be preferable, with another higher Tier to manage overall utilisation of the broad listing.

10.14 The PBAC noted the proposed 'administrative allowance' of [redacted]% above the estimates in the RSA (Tier 4) would provide a buffer to account for uncertainty in the utilisation estimates before a hard cap was effected. The PBAC noted it would be preferable to consider a set of estimates where there is sufficient certainty such that an allowance would not be necessary.

10.15 The PBAC considered that issues with the financial estimates would need to be resolved for a price volume agreement to be operate effectively.

Impact on other listings and RSAs

10.16 The PBAC noted that in creating a new RSA for a broad listing, pembrolizumab would need to be removed from some existing shared RSAs. This matter would be negotiated

with the Department in a post-PBAC process should a positive recommendation be made in the future.

Outcome:
Not recommended

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

MSD is disappointed by this decision. MSD partnered closely with clinicians and patient advocacy groups during the development of this submission to ensure it would improve affordable access to immunotherapy for Australian cancer patients. We hope to find clarity on a way forward during upcoming engagements with the PBAC and Department of Health in order to provide an equitable solution for Australian cancer patients.