

**6.11 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 The Category 2 submission requested a Section 100 Efficient Funding of Chemotherapy (EFC) Authority Required (Streamlined) listing for pembrolizumab for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) that it not curable by surgery or radiation.
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus cemiplimab.

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

Component	Description
Population	Metastatic or locally advanced cutaneous squamous cell carcinoma that is not curable by surgery or radiation.
Intervention	Pembrolizumab (200 mg IV) every 3 weeks or (400 mg IV) every 6 weeks
Comparator	Cemiplimab (350 mg IV) every 3 weeks
Outcomes	Objective response rate (ORR), Progression-Free Survival (PFS), Overall Survival (OS), Safety
Clinical claim	In patients with metastatic or locally advanced CSCC that is not curable by surgery or radiation, pembrolizumab is non-inferior to cemiplimab in terms of efficacy and safety.

Source: Table 1.1-1, p10 of the submission

CSCC, cutaneous squamous cell carcinoma; IV, intravenous; mg, milligram; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

2 Background

Registration status

- 2.1 Pembrolizumab was provisionally approved by the TGA on 20 September 2021 for recurrent or metastatic CSCC, and on the 2 May 2022 for locally advanced CSCC (expiring 15 September 2025 and 2 May 2024 respectively). The TGA indication is:
- KEYTRUDA (pembrolizumab) is indicated as monotherapy for the treatment of adult patients with recurrent or metastatic CSCC or locally advanced CSCC that is not curable by surgery or radiation.
- 2.2 Provisional approval was based on objective response rate and duration of response from a single arm study (KN629). The TGA noted that improvements in overall survival (OS), progression-free survival (PFS), or health related quality of life have not been

established¹. Full registration for this indication depends on submission of further clinical data to confirm clinical benefit. The sponsor indicated that final analysis from KN629 will be used to convert the current provisional to full approval in March 2024.

- 2.3 Pembrolizumab currently has TGA approval for melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), classical Hodgkin lymphoma (cHL), some urothelial carcinomas, some microsatellite instability high (MSI-HI) or mismatch repair deficit cancers, (dMMR) cancer, endometrial cancer, cervical cancer, renal cell carcinoma (RCC), oesophageal cancer, and triple-negative breast cancer.

Previous PBAC consideration

- 2.4 The nominated comparator, cemiplimab, was recommended for listing by the PBAC in the March 2022 PBAC meeting. The PBAC considered that, while the magnitude of difference in effectiveness of cemiplimab remains uncertain, there is a high unmet clinical need in this population with potential for quality of life benefits not encompassed in the available data. The PBAC’s recommendation for listing was based on, among other matters, its assessment that the subsequent uncertainty in the incremental cost-effectiveness ratio (ICER) could be addressed through a lower ICER threshold and resulting price reduction (para 7.2, cemiplimab, Public Summary Document (PSD), March 2022 PBAC meeting).
- 2.5 Cemiplimab is currently listed under a risk sharing arrangement. In March 2022, the PBAC advised that a risk sharing arrangement with a 100% rebate for utilisation above the agreed estimates would be necessary to minimise the high risk of cemiplimab use outside the proposed restriction (para 7.11, cemiplimab, PSD, March 2022 PBAC meeting).

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
Pembrolizumab					
Pembrolizumab 100 mg injection, 1 vial	\$7,886.09 (private) \$7,735.89 (public)	2	200 mg	6	KEYTRUDA MSD Australia Pty Ltd
Pembrolizumab 100 mg injection, 1 vial	\$15,640.65 (private) \$15,383.39 (public)	4	400 mg	3	KEYTRUDA MSD Australia Pty Ltd

Source: Table 1.4-1, p20 of the submission

Max, maximum; mg, milligram; no, number; Pty Ltd, proprietary limited; qty, quantity; Rpts; repeats

Note: These prices differ to those presented in the submission as they have been updated using the July 2023 pricing calculator

¹ Therapeutic Goods Association, Product Information, Pembrolizumab (2022).

Public Summary Document - November 2023 PBAC Meeting

Restriction Summary [new] / Treatment of Concept: [new]	
(For internal Dept. use)	Concept ID Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type <input checked="" type="checkbox"/> Authority Required (Streamlined)
	Severity: Metastatic or locally advanced
	Condition: Cutaneous squamous cell carcinoma
	Indication: Metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC)
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333
	Treatment Phase: Initial treatment
	Clinical criteria:
	The condition must be unsuitable for each of: (i) curative surgical resection, (ii) curative radiotherapy, AND
	Clinical criteria:
	Patient must have had a WHO performance status of 0 or 1, AND
	Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.	

	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND
	Clinical criteria
	The treatment must be the sole PBS-subsidised therapy for this condition.
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition AND
	Treatment criteria:
	Patient must not be undergoing treatment with this drug as a PBS benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 months from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs.

	Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – ‘Grandfather’ arrangements
	Clinical criteria:
	Patient must have received non-PBS treatment with this drug for this condition prior to [date of PBS listing],
	AND
	Clinical criteria:
	The condition must be unsuitable for each of: (i) curative surgical resection, (ii) curative radiotherapy
	AND
	Clinical criteria:
	Patient must have had a WHO performance status of 0 or 1 prior to initiation of non-PBS-subsidised treatment with this drug for this condition,
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	AND
	Treatment criteria:
	Patient must not be undergoing treatment with this drug as a PBS benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 months from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs.
	Prescribing instruction:
	A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria

Source: pp, 21-22 of the submission

CSCC, cutaneous squamous cell carcinoma; Dept, department; ID, identification; PBS, Pharmaceutical Benefits Scheme; WHO, World Health Organisation

- 3.1 The submission requested listing of two dosing schedules of pembrolizumab 200 mg IV every three weeks (Q3W) and 400 mg IV every 6 weeks (Q6W).
- 3.2 The prices presented were based on the current published Approved Ex-Manufacturer Price (AEMP) of \$3,823.75 per 100 mg vial of pembrolizumab PBS listed for other indications. This is higher than the price established in the CMA of \$3,645.00 per 100 mg vial. The submission stated that the published prices of pembrolizumab are used as the effective price of cemiplimab is not known to the sponsor. The pre-PBAC response stated that a Special Pricing Arrangement (SPA) would be requested for this listing, noting that there is also an SPA currently in place for cemiplimab.
- 3.3 The submission proposed a Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals, Authority Required (Streamlined) listing based on the justification that clinicians are likely to have extensive experience with pembrolizumab in the management of head and neck cancer or melanoma. This differs from the PBS listing for cemiplimab for the same patient population which is an Authority Required (telephone/online PBS Authorities system). Other PBS listings for pembrolizumab for other indications are Authority Required (Streamlined).
- 3.4 The requested indication (metastatic or locally advanced CSCC) is consistent with the current PBS listing for cemiplimab. The requested indication is narrower than the

provisional TGA indication which includes recurrent or metastatic CSCC (mCSCC) and locally advanced CSCC (laCSCC) patients. CSCC is susceptible to multiplicity of cancer sites, which means that cancers can arise in many locations independently, due to the common risk factor of ultraviolet (UV) light exposure. It may be difficult to correctly specify whether CSCC is a recurrence, or a secondary primary cancer site. The key pembrolizumab trial (KN629) included recurrent disease. Recurrent disease was not included in the cemiplimab studies.

- 3.5 The TGA approved Product Information (PI) states the proposed dosage of pembrolizumab for CSCC is 200 mg every 3 weeks or 400 mg every 6 weeks until disease progression or unacceptable toxicity. Patients without disease progression can be treated for up to 24 months or the equivalent number of treatment cycles. In the March 2022 consideration of cemiplimab (dosed every 3 weeks), the number of repeats permitted for initial treatment was reduced to two (providing 9 weeks of therapy in total), to better align with the median time for response (complete or partial response) observed in Study 1423 (1.94 months) and Study 1540 (2.07 months). The submission stated that the median time to response in KN629 was 2.0 months. Reducing the number of repeats for initial therapy from three to one for the 400 mg every 6 weeks dosing regimen (providing 12 weeks of therapy in total) and from six to two for the 200 mg every 3 weeks dosing regimen (providing 9 weeks of therapy in total) would better align with median time to response in KN629. In addition, changing the number of repeats for continuing therapy to be three for the 400 mg every 6 weeks dosing regimen and seven for the 200 mg every 3 weeks dosing regimen would allow 24 weeks of continuing therapy for both regimens. The current continuing restriction for cemiplimab for this indication allows for 24 weeks of continuing therapy.
- 3.6 If recommended, both pembrolizumab and cemiplimab will be available for metastatic or locally advanced CSCC. As no evidence was provided in the submission to support subsequent use of immunotherapy the addition of the following clinical criteria may be appropriate: 'Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition; or', 'Patient must have experienced a severe intolerance to the above therapy leading to permanent treatment discontinuation.' Flow on changes to the current cemiplimab initial therapy restriction for CSCC would also be required to restrict the use of subsequent immunotherapy in those who have already received such treatment unless they have experienced a severe intolerance leading to permanent treatment discontinuation.
- 3.7 The submission proposed a grandfather restriction for patients on cost-sharing programs who may be receiving pembrolizumab prior to PBS listing. This is consistent with the cemiplimab submission, however cemiplimab was the first immunotherapy agent available in this population. The submission stated that given the current availability of cemiplimab the number of grandfathered patients is expected to be minimal (<10 patients).

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

4 Population and disease

- 4.1 CSCC tends to affect the head and neck region owing to the large amounts of daily UV exposure to these anatomical regions. Consequently, the large growth and widespread dissemination of disease around this region can be disfiguring and significantly interfere with daily activities and quality of life². Over 95% of patients with CSCC who present with early disease are amenable to local therapy. Local therapies mainly consist of surgery and radiation or a combination of these modalities.
- 4.2 The proportion of individuals who develop laCSCC or mCSCC from earlier stage CSCC in Australia is uncertain, although small with international incidence estimates ranging from 1.2%³ to 3.7%⁴. Surgery and radiation will not be suitable for many patients with mCSCC or laCSCC due to disseminated disease or a contraindication to either surgery or radiation therapy. These patients tend to have poorer outcomes, with 5-year survival ranging between 50-70%⁵.
- 4.3 The patients who develop laCSCC or mCSCC are referred to a multidisciplinary consultation, where they may be assessed for their eligibility for either further local therapy or systemic therapy, such as immunotherapy. Those who go on to systemic therapy are likely to be treated with programmed cell death protein 1 (PD-1) inhibitors.
- 4.4 Pembrolizumab is a high-affinity antibody against PD-1, which is an immune-checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. The PD-1 immune-checkpoint pathway can be engaged by tumour cells to inhibit active T-cell immune surveillance. Pembrolizumab exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen-presenting or tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab reactivates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates anti-tumour immunity.

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

5 Comparator

- 5.1 The submission nominated cemiplimab 350 mg Q3W as the main comparator. The main arguments provided in support of this nomination were that cemiplimab is PBS

² Chen et al. (2007). *Predictors of skin-related quality of life after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma*. Arch Dermatol 143(11) 1386-1392

³ Nelson & Ashton. (2017). *Low incidence of metastasis and recurrence from cutaneous squamous cell carcinoma found in a UK population: Do we need to adjust our thinking on this rare but potentially fatal event?* J Surg Oncol, 116, 783-788.

⁴ Brougham et al. (2012). *The incidence of metastasis from cutaneous squamous cell carcinoma the impact of its risk factors*. Journal of surgical oncology, 106, 811-815

⁵ Lubov et al. (2021). *Prognostic factors of head and neck cutaneous squamous cell carcinoma: a systematic review*. Journal of otolaryngology – head & neck surgery 50:54

listed (November 2022) in the same patient population (metastatic or locally advanced CSCC that is not curative to surgery or radiation therapy) and is the current standard of care. The submission claimed in the context of the patient population and therapy most likely to be replaced in practice, cemiplimab is considered the main comparator to pembrolizumab. The ESC considered the choice of comparator was appropriate.

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 a health care professional (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from the health care professional noted patients with this condition are often frail with comorbidities and described a range of benefits of treatment with pembrolizumab including the option of dosing every 6 weeks minimising visits to hospital. The health care professional also indicated that prescribers would appreciate the option to treat new CSCC's despite prior use and highlighted the importance of multidisciplinary treatment management. The Melanoma & Skin Cancer Advocacy Network comments highlighted the psychosocial and economic impacts of CSCC and advised that it was important to have an additional 'tool in the toolbox' for patients for whom there are few options and prognosis is poor.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the pembrolizumab submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement).⁶

Clinical studies

6.4 No head-to-head randomised trials comparing pembrolizumab and cemiplimab were available.

6.5 The submission was based on an unmatched unanchored indirect comparison between four non-randomised, single-arm, open label studies in patients with laCSCC or mCSCC, who were not amenable to curative surgery or radiation:

⁶ Cherny NI, Dafni U, Bogaerts J, et al: *ESMO-Magnitude of Clinical Benefit Scale version 1.1*. Annals of Oncology 28:2340-2366, 2017

- CARSKIN (N=57): Phase 2 study evaluating the efficacy and safety of pembrolizumab. The laCSCC and mCSCC cohorts had a fixed-dose regimen of 200 mg Q3W for up to 35 administrations (approximately 24 months).
- KN629 (N=159): Ongoing Phase 2 study evaluating the efficacy and safety of pembrolizumab in participants with recurrent CSCC or laCSCC or mCSCC who were not amenable to surgery or radiation. All cohorts receive a fixed dose (200 mg Q3W) for up to 35 administrations (approximately 24 months). The results of the data cut in July 2020 were presented.
- Study 1540 (Group 1-3, N=193 and Group 6, N= 167): Ongoing Phase 2 study evaluating the efficacy and safety of cemiplimab. Groups 1 and 3 consist of a weight-based (3 mg/kg Q2W) and fixed-dose (350 mg Q3W) mCSCC cohort, respectively, Group 2 consists of laCSCC (3 mg/kg Q2W). The data cut of October 2020 was presented for Group 1-3. Group 6 is a confirmatory cohort using the fixed-dose (350 mg Q3W) regimen, the data cuts from April 2021 (N=84) and October 2021 (N= 167) were presented. Group 1-3 has previously been considered by the PBAC for cemiplimab in their March 2022 meeting.
- Study 1423 (N=26, Cohorts 7 and 8): Phase 1 study that evaluated the safety and preliminary efficacy of cemiplimab. Both cohorts received a weight-based dose (3 mg/kg Q2W) for up to 48 weeks. This study has previously been considered by the PBAC for cemiplimab in the March 2022 meeting.

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

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

Trial ID	Protocol title/ Publication title	Publication citation
Pembrolizumab studies		
CARSKIN NCT02883556	Maubec E, Boubaya M, Petrow P, et al. Phase II Study of Pembrolizumab As First-Line, Single-Drug Therapy for Patients With Unresectable Cutaneous Squamous Cell Carcinomas.	<i>J Clin Oncol.</i> 2020 Sep 10;38(26):3051-3061.
KN629 NCT03284424	A Phase 2, Open-label, Single-arm Study to Evaluate the Safety and Efficacy of Pembrolizumab in Participants with Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma (R/M cSCC) (KEYNOTE-629) Clinical Study Report (CSR) – Interim analysis 2. [KN629 CSR IA2]	July 2020
	Hughes BG, Munoz-Couselo E, Mortier L, et al. Pembrolizumab for locally advanced and recurrent/metastatic cutaneous squamous cell carcinoma (KEYNOTE-629 study): an open-label, nonrandomized, multicenter, phase II trial.	<i>Ann Oncol</i> 2021 Oct;32(10):1276-1285.
	Hughes BG, Mendoza RG, Basset-Seguín N, Vornicova O, Schachter J, Joshi A, Meyer N, Grange F, Piulats JM, Bauman JR, Chirovsky D. Health-related quality of life of patients with recurrent or metastatic cutaneous squamous cell carcinoma treated with pembrolizumab in KEYNOTE-629.	<i>Dermatology and Therapy.</i> 2021 Oct; 11:1777-90.
	Grob JJ, Gonzalez R, Basset-Seguín N, et al. Pembrolizumab Monotherapy for Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma: A Single-Arm Phase II Trial (KEYNOTE-629).	<i>J Clin Oncol.</i> 2020 Sep 1;38(25):2916-2925.

Trial ID	Protocol title/ Publication title	Publication citation
Cemiplimab studies		
Study 1540 NCT02760498	Cemiplimab EPAR Public Assessment Report 2022. Data cut-off in October 2020.	October 2020
	Rischin D, Khushalani NI, Schmults CD, et al. Integrated analysis of a phase 2 study of cemiplimab in advanced cutaneous squamous cell carcinoma: extended follow-up of outcomes and quality of life analysis.	<i>J Immunother Cancer.</i> 2021 Aug;9(8): e002757.
	Rischin D, Migden MR, Lim AM, et al. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing.	<i>J Immunother Cancer.</i> 2020 Jun;8(1): e000775.
	Migden MR, Khushalani NI, Chang ALS, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial.	<i>Lancet Oncol.</i> 2020 Feb;21(2):294-305.
	Migden MR, Schmults C, Khushalani N, et al. Phase II study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (CSCC): Final analysis from Study 1540 groups 1, 2 and 3.	<i>Ann Oncol,</i> 2022 33, S918-S919.
	Hughes BG., Grob, JJ, Bowyer, SE et al. Phase II confirmatory study of cemiplimab (350mg IV Q3W) in patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC): Study 1540 Group 6.	<i>Ann Oncol,</i> 2022 33, S921.
Study 1423 NCT02383212	Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, Chung CH, Hernandez-Aya L, Lim AM, Chang AL, Rabinowits G. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma.	<i>N Engl J Med.</i> 2018 Jul 26;379(4):341-51.

Source: Table 2.2-2 and Table 2.2-3, pp30-31 of the submission.

Ann, Annals; Aug, August; Clin, clinical; CSCC, cutaneous squamous cell carcinoma; CSR, clinical study report; Eng, England; EPAR, European public Assessment Report; Feb, February; IA2, interim analysis 2; Immunother, immunotherapy; IV, intravenous; J, Journal; Jul, July; Med, medicine; mg, milligram; Oct, October; Oncol, Oncology; PD 1, programmed cell death protein 1; Sep, September; Q3W, every 3 weeks; R/M, recurrent or metastatic.

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

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ median duration of follow up (range)	Risk of bias	Patient population	Outcome(s)
Pembrolizumab studies					
CARSKIN	57	Phase II, SA, OL, MC 22.4 months	High	laCSCC or mCSCC, not amenable for curative surgery or radiation therapy (Chemotherapy naïve)	Primary: ORR Secondary: OS, PFS and safety
KN629	159	Phase II, ongoing, SA, OL, MC 15.3 months (0.4 - 31.8 months)	High	laCSCC or mCSCC or recurrent CSCC, not amenable for curative surgery or radiation therapy	Primary: ORR Secondary: OS, PFS and safety
Cemiplimab studies					
Study 1540	Group 1-3 193	Phase II, ongoing, SA, OL, MC Group 1-3: 15.7 months (0.6 – 43.2 months) Group 6: 8.7 months (0.0 – 19.5 months)	High	laCSCC or mCSCC, not amenable for curative surgery or radiation therapy	Primary: ORR Secondary: OS, PFS and safety
	Group 6 167				
Study 1423	26	Phase I, SA, OL, MC 11.0 months (1.14 – 17.0 months)	High	laCSCC or mCSCC, not amenable for curative surgery or radiation therapy	Primary: Safety Secondary: ORR, OS and PFS

Source: Table 2.4-9 and Table 2.4-13, p79-89 of the submission, and Table S1 (Migden et al. 2018).

CSCC, cutaneous squamous cell carcinoma; laCSCC, locally advanced cutaneous squamous cell carcinoma; MC, multi-centre; mCSCC, metastatic cutaneous squamous cell carcinoma; OL, open label; ORR, Objective response rate; OS, overall survival; PFS, progression-free survival; SA, single arm.

- 6.8 The ESC noted that all four studies were assessed as high risk of selection and performance bias (single arm cohorts, non-comparative, non-randomised allocation and unblinded participants and personnel), moderate risk of attrition bias and low risk of detection and reporting bias. Therefore, the overall risk of bias is high. The high overall risk of bias for Study 1540 and Study 1423 is consistent with the high risk of bias assessment during PBAC’s consideration of cemiplimab (Table 4, cemiplimab, PSD, March 2022 PBAC meeting).
- 6.9 A claim of non-inferiority for pembrolizumab over cemiplimab was based on the efficacy and safety outcomes of ORR, PFS, OS, and adverse events using an unmatched, unanchored indirect comparison.
- 6.10 Differences in the baseline characteristics between studies, study design, sample size and duration of follow-up between studies were identified to be important transitivity concerns and could confound the results of the indirect comparisons.
- 6.11 The included studies differed on a number of inclusion and exclusion criteria which can impact the populations considered across cohorts and studies:
- KN629 included patients with locally recurrent disease who did not have metastatic disease and ‘recurrent’ population was not considered in the other studies. There were 47 patients (29.6% of total population in KN629) with recurrent disease and these patients were analysed with mCSCC as a cohort.
 - CARSKIN and Study 1423 only included patients who were required to be ineligible or not amenable to surgery, while KN629 and Study 1540 require patients to be ineligible for either surgery or radiation therapy.

- The recurrent/metastatic cohort in KN629 and mCSCC cohort in Study 1423 only included distant metastasis, whereas Study 1540 included distant and regional metastatic disease.
 - KN629 allowed patients with regional nodal metastatic disease to be enrolled in the laCSCC cohort, whereas in Study 1540, these patients were included in the mCSCC cohort. Similarly, Study 1423 included patients with regional metastatic disease in the laCSCC cohort.
 - CARSKIN and KN629 excluded patients with active autoimmune disease within 2 years while Study 1540 and Study 1423 excluded those who had this condition within 5 years.
 - CARSKIN and KN629 excluded patients who received immunosuppressive therapy within 7 days prior to the first dose of the study drug, while Study 1540 and Study 1423 excluded these patients when they received this therapy within 4 weeks prior to the first dose of the study drug.
- 6.12 The exclusion of patients with active autoimmune disease and immunosuppression is not specified in the proposed PBS restriction. Immunosuppression has been associated with poorer outcomes in patients with CSCC (HR 2.66, 95% CI: 2.26, 3.13) in a meta-analysis by Sahoalier et al. (2019). This may lead to lower treatment effect of pembrolizumab in these patients.
- 6.13 The ESC noted there were important differences in the baseline characteristics across the studies which raised concerns regarding the validity of the indirect comparison.
- All studies included eligibility criteria requiring patients to have an ECOG PS 0 to 1. There were a higher proportion of patients with ECOG PS 1 in KN629 (63.5%) compared to the cemiplimab studies (range from 55.4% to 61.5% across Study 1540 Group 1-3 and Study 1423). CARSKIN had 54.4% patients with ECOG PS 1. This difference may bias the results in favour of cemiplimab.
 - There were a higher proportion of patients with primary tumour staging \geq T2 and nodal staging \geq N2 in KN629 (73% and 32.1%, respectively) compared to Study 1540 Group 1-3 (59.6% and 27.5%, respectively). This may bias the results in favour of cemiplimab. Data for CARSKIN and Study 1423 were not reported.
 - There were a lower proportion of patients with metastasis staging M1 in KN629 compared to Study 1540 Group 1-3 (36.5% vs 45.6%) that may bias the results in favour of pembrolizumab.
 - There were a higher proportion of patients with prior systemic therapy in KN629 (64.8%) compared to Study 1540 Group 1-3 (33.7%) and Study 1423 (57.7%), whilst CARSKIN consisted of patients who were treatment naïve only. The direction of impact of this difference is uncertain.
 - There were differences in the median age and proportion of female patients in pembrolizumab studies (74-79 years and 19.3-25.2%, respectively) compared with

cemiplimab studies (72-76 years and 16.6-22.1%, respectively). The impact of these differences is uncertain.

- Given these differences, a comparison of pembrolizumab and cemiplimab without baseline adjustments are potentially biased due to confounding.
- 6.14 The timing of outcome assessment differed across studies. While ORR was measured at similar time points in KN629 and Study 1540 (every 6 weeks in the first year and every 9 weeks in the second year), Study 1423 measured ORR every 8 weeks and CARSKIN at Week 9, Week 15, Week 24 and every 12 weeks thereafter. There is a potential that more frequent assessments (evaluation bias)⁷ in KN629 and Study 1540 (and Study 1423) may have captured more responses at the data cut-off compared with CARSKIN.
- 6.15 The pembrolizumab study KN629 was to be analysed on the basis of all participants as treated (APaT). All enrolled patients were included in the analysis (100%) and hence in this study was equivalent to an ITT analysis.
- 6.16 Overall, the median treatment exposure was longer for cemiplimab (11.8 months, at 15.7 months follow-up in Study 1540 Groups 1-3; 8.3 months, at 11 months follow-up in Study 1423) than for pembrolizumab (6.9 months, at 15.3 months follow-up in KN629, not specified in CARSKIN). The ESC noted that in the recurrent/metastatic cohort in KN629, 2 (1.9%) of participants remained on pembrolizumab with median and mean treatment exposures of 5.8 months and 10.5 months respectively. In the Study 1540 Group 1 and Group 3 mCSCC cohorts the mean treatment exposures reported were 13.0 months and 11.7 months respectively. In the laCSCC cohort of KN629, 20 (37.0%) of participants remained on pembrolizumab with median and mean treatment exposures of 9.3 months and 8.3 months respectively. The overall discontinuation rate was observed to be higher in the pembrolizumab study KN629 (73.6%) compared to the cemiplimab Study 1540 Group 1-3 (65.8%). The main reasons for discontinuation were progressive disease (30.2% in KN629, 29% in Study 1540) and adverse events (18.9% in KN629, 10.4% Study 1540). KN629 and Study 1540 are ongoing. The estimated study completion date for KN629 is September 2023. The ESC considered that it was difficult to estimate a treatment exposure for the laCSCC cohort of KN629 due to the number of patients remaining on treatment. The ESC noted that the mean treatment exposure for the recurrent/metastatic cohort in KN629 was lower than that reported for Group 1 and Group 3 of Study 1540. However, the ESC agreed with the Pre-Sub-Committee Response (PSCR) that the differences may reflect a more aggressive and comorbid population recruited to KN629 compared to Study 1540.

⁷ Villaruz, Liza C., and Mark A. Socinski, (2013), The clinical viewpoint: definitions, limitations of RECIST, practical considerations of measurement. *Clinical cancer research*. 19(10),2629-2636.

- 6.17 CARSKIN, KN629 and Study 1540 were considered to have met their primary objectives if ORR passed the study clinically meaningful threshold (ORR exceeded 15-28%). No clinically meaningful threshold was specified for Study 1423.
- 6.18 The submission did not propose a non-inferiority margin. The absence of non-inferiority margin makes it difficult to assess the non-inferior clinical claim with certainty.

Comparative effectiveness

- 6.19 The evidence of pembrolizumab effectiveness and safety was based on unmatched indirect comparisons (without a common reference arm) with no formal statistical analyses. The assessments are simply outcome comparisons across studies and not a comparison of treatment effect across studies. Results need to be interpreted with caution given the potential for bias from both observed and unobserved cross-study differences.
- 6.20 The submission and PSCR contended that a matched adjusted indirect comparison (MAIC) was not appropriate due to the lack of complete data on baseline characteristics such as prognostic factors and treatment effect modifiers, and conducting MAIC without the inclusion of these factors may lead to residual bias from the unaccounted covariates. The comparisons between pembrolizumab and cemiplimab presented in the submission were descriptive.
- 6.21 Table presents the ORR, PFS and OS reported for each study.

Table 4: Results of ORR, PFS and OS across the studies

Proportion of patients, n (%)	Pembrolizumab		Cemiplimab		
	CARSKIN N= 57	KN629 N= 159	Study 1540 Group 1-3 N= 193	Study 1540 Group 6 ^b N=167	Study 1423 N= 26
DCO	Dec 2019	Jul 2020	Oct 2020	Oct 2021	Oct 2017
Response					
Number included in analysis	57	159	193	164	26
ORR (CR + PR), n (%)	24 (42)	64 (40.3)	91 (47.2)	74 (45.1)	13 (50)
95% CI ^a	(29, 56)	(32.6, 48.3)	(39.9, 54.4)	(37.4, 53.1)	(30,70)
Progression Free Survival					
Number included in analysis	39 ^c	159	193	165	26
Number of events, n (%)	NS	93 (58.5)	101 (52.3)	NS	12 (46.2)
Median, months (95% CI) ^a	6.7 (3.45-NE)	7.8 (5.3, 12.3)	18.5 (10.3, 31.3)	14.7 (10.4-NE)	22.0 (5.4, 31.4)
Estimated event free probability, % (95% CI) ^a					
6 months	NS	53.3 (45.0,60.9)	66.7 (59.2, 73.1)	NS	71.8 (49.7, 85.5)
12 months	NS	42.4 (34.3, 50.2)	55.8 (48.1, 62.8)	NR	67.3 (45.0, 82.2)
24 months	NS	NS	46.9 (39.2, 54.3)	NS	25.2 (1.8, 62.4)
Overall Survival					
Number included in analysis	39 ^c	159	193	165	26
Number of events, n (%)	NS	73 (45.9)	61 (31.6)	NS	9 (34.6)
Median, months (95% CI) ^a	24.9 (14.2-NE)	26.4 (19.5, NR)	NR	NR (17.6-NE)	NR (16.2, NE)
Estimated probability of survival, % (95% CI) ^a					
6 months	81.3 (69.7, 94.8)	81.0 (74.0, 86.3)	88.9 (83.5, 92.6)	NS	88.0 (67.1, 96.0)
12 months	75.5 (62.7, 90.8)	65.1 (57.1, 72.0)	82.8 (76.6, 87.6)	NR	83.3 (61.3, 93.4)
24 months	NS	52.7 (43.8, 60.9)	73.1 (66.0, 78.9)	NS	60.2 (37.2, 77.0)

Source: Table 2.4-9, Table 2.5-3, Table 2.5-5 and Table 2.5-6, p79, p96, p102 and p105 of submission.

CI, confidence interval; CR, complete response; Dec, December; DCO, data cut off; Jul, July; N, number; NE, not evaluable; NR, not reached; NS, not specified; Oct, October; ORR, objective response rate; OS, overall survival; PR, partial response; PFS, progression free survival.

^a Clopper Pearson method exact confidence interval for binomial data

^b The submission presented efficacy and safety outcomes results from two data cuts (April 2021 and October 2021) for Group 6 in Study 1540. Results from the most recent data cut in October 2021 (where available) are presented given that this included all participants who were enrolled and received the first dose of treatment. DCO in April 2021 only reported results for 84 patients.

^c Only primary cohort (n=39) was reported for PFS and OS in CARSKIN.

6.22 CARSKIN, KN629 and Study 1540 passed their respective study clinically meaningful thresholds for ORR. The ORR reported for the total populations of pembrolizumab studies (42% in CARSKIN and 40.3% in KN629) were numerically lower compared to cemiplimab studies (47.2% in Group 1-3 and 45.1% in Group 6 in Study 1540 and 50% in Study 1423).

- 6.23 The median PFS was numerically lower in pembrolizumab studies (7.8 months in KN629 and 6.7 months in CARSKIN) compared with cemiplimab studies (18.5 months in Group 1-3 and 14.7 months in Group 6 in study 1540 and 22 months in Study 1423).
- 6.24 The median OS reported in pembrolizumab studies were 26.4 months for KN629 and 24.9 months in CARSKIN, whilst the median OS was not reached for cemiplimab studies. When comparing the number of deaths across studies, pembrolizumab KN629 was observed to have a higher proportion of events (ranging from 25.9% to 56.2% across cohorts) compared to cemiplimab Study 1540 (ranging from 19.2% to 41.1%). The cemiplimab studies had higher 12 month OS (82.8% in Group 1-3 of Study 1540 and 83.3% in Study 1423) compared to pembrolizumab studies (75.5% in CARSKIN and 65.1% in KN629).
- 6.25 Overall, ORR, PFS and OS results appear to favour cemiplimab over pembrolizumab. Results are potentially confounded by important transitivity concerns described above.
- 6.26 The submission stated that the differences in PFS and OS between pembrolizumab and cemiplimab studies are highly likely to be driven by the differences in the baseline characteristics (as described in paragraphs 6.11 and 6.13).
- 6.27 Differences identified in the baseline characteristics between studies could potentially favour cemiplimab or pembrolizumab. There are substantial issues relating to study design, sample size and transitivity that may not allow a meaningful conclusion to be reached on the comparative effectiveness and safety of pembrolizumab versus cemiplimab. As such, the evaluation considered the results should be interpreted with caution given the uncertainty on the direction and magnitude of impact of the identified factors on observed outcomes.

Comparative harms

- 6.28 The table below summarises the key adverse events (AEs) from the four single-arm studies. The submission reported treatment related adverse events (TRAE) for most studies, except for Group 6 in Study 1540, where TEAE were reported.

Table 5: Summary of key adverse events across the studies

Adverse events	Pembrolizumab		Cemiplimab		
	CARSKIN LA/M N=57	KN629 LA/R-M N=159	Study 1540 Group 1-3 N=193	Study 1540 Group 6 N=167	Study 1423 LA/M N=26
DCO	Dec 2019	Jul 2020	Oct 2019	Oct 2021	Oct 2017
Median treatment exposure (months)	NS	6.9	11.8	8.2	8.3
Number included in the analysis	55	159	193	165	26
Treatment related adverse events, n (%)					
Any grade	39 (71)	110 (69.2)	148 (76.7)	75 (98.8) ^a	15 (57.7)
Grade ≥3	4 (7.2) ^b	19 (11.9)	33 (17.1)	75 (45.5) ^a	5 (19.2)
Led to discontinuation	6 (10.9)	14 (8.8)	16 (8.3) ^c	23 (13.9) ^a	2 (7.7)
Led to death	2 (3.6)	2 (1.3)	1 (0.5)	14 (8.5) ^a	0
Grade ≥3, incidence ≥5%, n (%)					
Increased ALT	NS	4 (2.5)	0	NS	1 (3.8)
Increased AST	NS	4 (2.5)	1 (0.5)	NS	1 (3.8)
Colitis	1 (2)	2 (1.3)	2 (1.0)	NS	NS
Diarrhoea	1 (2)	0	2 (1.0)	NS	0
Immune-related adverse events, incidence ≥0.5%, n (%)					
Any grade	NS	36 (22.6)	57 (29.5)	NS	NS
Grade ≥3	NS	13 (8.2)	18 (9.3)	NS	NS
Any grade, incidence ≥0.5%, n (%)					
Hypothyroidism	NS	14 (8.8)	21 (10.9)	NS	NS
Pneumonitis	NS	6 (3.8)	12 (6.2)	NS	NS
Severe skin reactions/Rash	NS	5 (3.1)	2 (1.0)	NS	NS

Source: Table 2.5-9, Table 2.5-10, Table 2.5-11, Table 2.5-12 and Table 2.5-13, p112-115 of submission.

Abbreviations: ALT, alanine transaminase (liver enzyme); AST, aspartate transaminase (liver enzyme); DCO, data cut-off; LA, locally advanced; M, metastatic; NS, not specified; R-M, recurrent or metastatic TEAE, Treatment emergent adverse events; TRAE, Treatment related adverse events.

^a Reported as TEAE. TRAE data was unavailable for Group 6.

^b Corrected during the evaluation. Estimate in submission was 7.7%

^c Data from DCO Oct 2020 (Cemiplimab EPAR 2022) as TRAE leading to discontinuation from DCO October 2019 was unavailable. TEAE leading to discontinuation was reported in 19 patients (9.8%) in DCO October 2019 (Rischin et al. 2021).

- 6.29 The proportion of Grade 3-5 TRAEs were numerically lower in the pembrolizumab studies (7.7% in CARSKIN to 11.9% in KN629) compared to the cemiplimab studies (17.1% in Group 1-3 of Study 1540 and 19.2% in Study 1423).
- 6.30 Discontinuation and death due to TRAEs were slightly higher in CARSKIN (10.9% and 3.6% respectively) and KN629 (8.8% and 1.3% respectively) compared to Group 1-3 in Study 1540 (8.3% and 0.5% respectively) and Study 1423 (7.7% and 0% respectively).
- 6.31 The ESC previously considered that the fixed-dosing regimen of cemiplimab (Groups 3 and 6 of Study 1540) would result in a higher cemiplimab dose than weight-based dosing (Groups 1 and 2 of Study 1540 and Study 1423) for some patients and as such may increase the risk of adverse events in those patients. Hence, the ESC previously considered that the adverse event data reported in the cemiplimab submission (Group 1-3) may not be truly reflective of the risk of events in clinical practice (para 6.32, cemiplimab, PSD, November 2020 PBAC meeting).

Benefits/harms

6.32 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

6.33 The submission described pembrolizumab as non-inferior in terms of effectiveness compared to cemiplimab. The evaluation considered this claim was highly uncertain given the transitivity issues and the absence of a non-inferiority margin in the unmatched, unanchored indirect comparison used as the evidence base:

- The high risk of bias associated with the results due to the unmatched, unanchored indirect comparison of single-arm studies with small sample sizes, different duration of follow-up and treatment exposure.
- There were key differences in the eligibility criteria between studies. KN629 included patients with locally recurrent disease who did not have metastatic disease (29.6% of total population), which is different to the proposed PBS population. The definitions used for laCSCC and mCSCC differed across studies which may impact the ability to make formal comparisons.
- There were key differences in the baseline characteristics between pembrolizumab and cemiplimab studies such as age, sex, ECOG PS, primary tumour site and staging, nodal disease involvement, metastasis staging, prior radiation and prior systemic therapy that raised transitivity concerns and may bias results in favour of cemiplimab or pembrolizumab. The PSCR continued to argue that the differences between studies bias in favour of cemiplimab due to pembrolizumab having a prognostically poorer patient population overall. The ESC considered the direction and magnitude of the impact of the differences in baseline characteristics on outcome results was unknown.
- The ORR, PFS and OS outcomes reported for the total populations of pembrolizumab studies were numerically lower compared to cemiplimab studies. Overall, these results appear more favourable for cemiplimab over pembrolizumab.

6.34 The submission described pembrolizumab as non-inferior in terms of safety compared to cemiplimab. This claim was highly uncertain given the transitivity issues, small sample sizes, different duration of follow-up and treatment exposure as described above.

6.35 The ESC recalled that in the March 2022 consideration of cemiplimab, the PBAC had advised that the claim of superior comparative effectiveness versus best supportive care with or without chemotherapy was uncertain but considered it was reasonable in the context of a condition with high clinical need and a lack of alternative treatment options (para 6.45, cemiplimab, PSD, March 2022 PBAC meeting). The ESC considered the listing of cemiplimab reduced the high clinical need for treatment options.

However, while acknowledging the limitations of the available evidence, the ESC considered that the clinical claims of non-inferior efficacy and non-inferior safety of pembrolizumab versus cemiplimab were uncertain but likely reasonable.

- 6.36 The PBAC considered that the claim of non-inferior comparative effectiveness was uncertain but likely reasonable.
- 6.37 The PBAC considered that the claim of non-inferior comparative safety was uncertain but likely reasonable.

Economic analysis

- 6.38 The submission presented a CMA of pembrolizumab versus cemiplimab based on the claim of non-inferior efficacy and safety. The CMA presented was based on the published price for cemiplimab.
- 6.39 The equi-effective doses were estimated as:
- pembrolizumab 200 mg Q3W is equivalent to cemiplimab 350 mg Q3W, and
 - pembrolizumab 400 mg Q6W is equivalent to 2x cemiplimab 350 mg Q3W.
- 6.40 The submission indicated that the PBAC previously recommended cemiplimab based on the fixed dosing regimen of 350 mg Q3W, so used 350 mg Q3W in the CMA. An alternate weight-based dosing regimen of cemiplimab, IV 3 mg/kg every 2 weeks was used for Groups 1 and 2 of Study 1540 and Study 1423 of the cemiplimab trials presented in the clinical evidence.
- 6.41 The proposed equi-effective doses are consistent with the recommended doses in the TGA PI for both pembrolizumab and cemiplimab.
- 6.42 In claiming that the equi-effective doses are the recommended doses of each drug, the submission implicitly assumed the same treatment duration for both pembrolizumab and cemiplimab. The CMA was based on a treatment duration of one year (12 months). The submission contended that given different treatment durations between trials and cohorts and that DUSC had considered 57.97 weeks applied for cemiplimab (Table 14, cemiplimab, PSD, March 2022 PBAC meeting) on overestimate, the submission based the costs on an annual basis. Studies KN629 and Study 1540 used to support the non-inferiority claim are ongoing and follow-up remains incomplete. Data on the total dose required over the duration of these trials are not yet available.
- 6.43 Overall, the mean treatment exposure was longer for cemiplimab (11.7 months, at 18.5 months follow-up in Study 1540 (Groups 1-3)) than for pembrolizumab (9.7 months, at 15.7 months follow-up in KN629). However, the ESC considered the differences observed could be due to differences in trial inclusion and exclusion criteria, patient baseline characteristics and proportion remaining on treatment at the time of the analysis (see paragraph 6.16).

- 6.44 The submission assumed there were no differences in the prescribing and administration profiles of pembrolizumab and cemiplimab, apart from the difference in dosing frequency for pembrolizumab 400 mg Q6W that would result in a reduction in administration cost. This cost offset (approximately \$994) was small relative to the total medicine and administrative cost per year.
- 6.45 The submission assumed there would be no differences in the safety profiles between pembrolizumab and cemiplimab, thus there would be no additional costs or cost offsets in the listing of pembrolizumab. The evaluation considered this may be reasonable given that both drugs are from the same therapeutic class and patients are likely to be managed in a similar approach irrespective of the type of immunotherapy. Treatment related Grade ≥ 3 AEs were numerically lower in the pembrolizumab studies compared to the cemiplimab studies and there were numerically more AEs leading to discontinuation (8.8-10.9% vs 7.7-8.3%) and deaths (1.3-3.6% vs. 0 to 0.5%) for pembrolizumab and cemiplimab respectively. Given the unmatched, unanchored indirect nature of the comparison with differences across study design, populations, prior therapies and treatment exposure duration, a meaningful conclusion relating to the comparative safety of pembrolizumab and cemiplimab is difficult and highly uncertain.
- 6.46 The results of the CMA (Q3W dosing) and sensitivity analysis (Q6W dosing) based on the published AEMP of cemiplimab are presented in Table 6.

Table 6: Results of the cost-minimisation (Q3W dosing) and sensitivity analysis (Q6W dosing) based on published AEMP

Component	Pembrolizumab 200 mg Q3W	Pembrolizumab 400 mg Q6W	Cemiplimab 350 mg Q3W
Cost per vial (AEMP)	\$3,645.00	\$3,674.58	\$7,290.00 ^a
Vials per dose	2	4	1
Dose duration	1 year	1 year	1 year
Vials per year ^b	34.79	34.79	17.39
Administration cost per dose ^c	\$118.30	\$118.30	\$118.30
Administrations per year ^d	17.39	8.70	17.39
Total medicine cost and administration per year	\$128,851.50	\$128,851.50	\$128,851.50
Difference in cost per year	\$0	\$0	\$0

Source: Compiled from information presented in Table 3.4-1, p131 of the submission and updated to reflect current MBS prices
AEMP, approved ex-manufacturer price; mg, milligram; Q3W, every 3 weeks; Q6W, every 6 weeks

^a Based on published price in May 2023 [<https://www.pbs.gov.au/info/industry/pricing/ex-manufacturer-price>]

^b Estimated (maximum) number of required vials based on recommended dosing

^c Based on MBS item number 13950– updated to reflect current prices

^d Based on recommended dosing (for example, $365.25/21=17.39$)

- 6.47 The submission noted that the cost per 100 mg vial of pembrolizumab would be \$3,645.00 based on the comparison of the Q3W regimens. A comparison based on the Q6W regimen was provided in the submission as a sensitivity analysis. The submission also acknowledged that the effective price and cost per patient will be lower than the numbers presented in this CMA, which are based on published prices.
- 6.48 The evaluation considered there is uncertainty in the estimating of equi-effective doses due to the different durations of follow-up and treatment exposure and number

of doses administered across the studies. Moreover, studies KN629 and 1540 are ongoing therefore data on these parameters are incomplete. If pembrolizumab requires a higher number of doses compared to cemiplimab, this would result in a lower cost-minimised price for pembrolizumab. The PSCR argued that the duration of treatment for pembrolizumab is expected to be similar to cemiplimab. The ESC noted that the CMA draws from a limited clinical evidence base that used an unmatched, unanchored indirect comparison. The ESC agreed with the evaluation that there is uncertainty in estimating the equi-effective doses but considered that the evidence available indicated that the financial risk to the Government of the treatment duration for pembrolizumab being longer than cemiplimab was low.

Pembrolizumab cost/patient/year

- 6.49 The estimated average cost per patient per year for pembrolizumab was \$136,006 (published DPMA proposed in submission with a public/private split of 24.74% / 75.36%). This increases to \$136,048 using the 1 July 2023 mark-ups and dispensing fee. The estimated average published cost per patient per year for pembrolizumab would be \$129,786 if the calculated cost-minimised price was applied.

Estimated PBS usage & financial implications

- 6.50 This submission was not considered by DUSC.
- 6.51 The submission used an epidemiological approach to estimate the predicted use and cost of the requested listing of pembrolizumab for patients with laCSCC or mCSCC that is not amenable to curative surgery or radiation. The evaluation considered an epidemiological approach is appropriate because there is likely insufficient PBS utilisation data on cemiplimab to undertake a market share approach given its recent PBS listing in November 2022.
- 6.52 Cemiplimab is currently listed under a Risk Sharing Arrangement (see paragraph 6.66). The submission stated that the current financial caps for cemiplimab may not reflect the CSCC burden in Australia. As such, a number of key parameters related to the incidence of CSCC, laCSCC and mCSCC were revised by the submission from inputs used in the cemiplimab submission considered by the PBAC in March 2022. This resulted in a difference in the estimated patient numbers between the two submissions. A comparison of inputs used for the financial estimates in the pembrolizumab submission and the cemiplimab submission is presented in Table 7.

Table 7: Difference in inputs to financial estimates for cemiplimab March 2022 and pembrolizumab November 2023

Inputs	Cemiplimab submission (March 2022)	Pembrolizumab submission (November 2023)
Prevalence rate of CSCC in Australia	0.70% in Year 1	-
Incidence rate of CSCC in Australia	0.69% in Year 2 to 0.70% in Year 6	0.777%
Proportion of patients with laCSCC and mCSCC	1.4% incident patients 1.67% prevalent patients	3.7%
Incidence of laCSCC or mCSCC who progress from early stages	3.34%	-
Proportion of patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation	45%	45%
Proportion of patients with ECOG performance status 0-1	83.3%	83.3%
Uptake rates	70% in Year 1, 80% in Year 2 and 90% in Years 3 to 6	80% in Year 1, 90% in Year 2 to 6
Mean treatment duration	57.97 weeks	13.1 months (56.92 weeks)
Dosing schedule	Q3W	Q3W for 7 cycles (initiating) Q6W for 5.99 cycles (continuing)

Source: Compiled during commentary using data from cemiplimab Public Summary Document (March 2022 PBAC meeting) and Section 4.1 and 4.2 of the submission

ECOG, Eastern Cooperative Oncology Group; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; Q3W, every 3 weeks; Q6W, every 6 weeks.

6.53 The key inputs in the financial analysis are summarised in Table 8.

Table 8: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Incidence of CSCC	0.777%	Wilson et al., 2022	The Wilson et al., 2022 study, was conducted in South-eastern New South Wales and included a relatively small sampling area (population estimate n=342,247) of which 74.3% came from a single coastal town. Furthermore, 35% of the population of this region was aged over 60 years. This brings into question the generalisability of these findings. This value is larger than the incidence rate used in the cemiplimab March 2022 submission which utilised data from the NCCI survey (see Table 7). Incidence of CSCC may be overestimated.
Proportion of CSCC that develop laCSCC or mCSCC	3.7%	Brougham et al. 2012	This was based on a New Zealand study and is higher than the incidence rate used in the cemiplimab March 2022 submission, which were 1.4% and 1.67% for incident and prevalent patients respectively (see Table 7). The cemiplimab submission estimates were based on UK data from Venables et al., 2018. The submission reported that the UK estimates were likely underestimated and therefore presented the New Zealand rate of 3.7% as the base case. Available literature reports incidences between 1.2% to 3.7% (Brougham et al (2012), Nelson & Ashton (2017)).
Proportion of patients not	45%	Ronconi 2020, IQVIA research	This value is consistent with the value used in the cemiplimab submission (see Table 7).

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Data	Value	Source	Comment
eligible for curative surgery or radiation			
Proportion of patients with ECOG performance status 0-1	83.3%	Para 6.78, cemiplimab, PSD, March 2022 PBAC Meeting	This is consistent with the estimate of 16.7% for participants with an ECOG PS of ≥ 2 submission suggested by the PBAC in their consideration for cemiplimab (para 7.10, cemiplimab, PSD, March 2022 PBAC meeting).
Treatment utilisation			
Uptake rate	Yr 1: 80% Yr 2: 90% Yr 3: 90% Yr 4: 90% Yr 5: 90% Yr 6: 90%	Para 6.1, cemiplimab, PSD, March 2022 PBAC Meeting	This was based on estimates for cemiplimab with an uptake rate of 70% in year 1 increasing to 90% in years 3-6 (see Table 7).
Treatment duration	13.1 months	Para 6.63, cemiplimab, PSD, March 2022 PBAC Meeting	The submission assumed that the mean treatment duration for cemiplimab and pembrolizumab will be the same. It is unclear whether treatment duration would be equal.
Number of cycles per dosing schedule	Q3W – 7 Q6W – 5.99	Assumption	The submission assumed patients would most likely be treated initially with 200 mg Q3W dosing schedule and once stable and progression free they may move to 400 mg Q6W dosing schedule. The assumed total duration of treatment was 56.92 weeks (13.1 months) and the submission assumed 21 weeks of initiating (Q3W) treatment and 35.92 weeks of continuing (Q6W), 7 and 5.99 cycles of Q3W and Q6W respectively. The submission did not provide evidence to support the assumption that patients would start on a Q3W dosing schedule and move to Q6W dosing. However, sensitivity analysis conducted during the evaluation to test the impact of Q6W dosing assumptions indicated they did not have a significant impact on the financial estimates.
Costs			
Pembrolizumab initiating	AEMP: \$7,648 DPMQ: \$7,848.93 ^a	Based on pembrolizumab 200 mg Q3W dosing	The price applied for the financial estimates was the current published AEMP for pembrolizumab (\$3,824 per 100 mg vial) for other PBS listed indications. It is higher than the cost-minimised price established of AEMP \$3,645 (DPMQ \$7,487.66).
Pembrolizumab continuing	AEMP: \$15,295 DPMQ: \$15,577.00 ^a	Based on pembrolizumab 400 mg Q6W dosing	The price applied for the financial estimates was the current published AEMP for pembrolizumab (\$3,824 per 100 mg vial) for other PBS listed indications. It is higher than the cost-minimised price established of AEMP \$3,645 (DPMQ \$14,854.47).
Cemiplimab	Not included		The submission presented the estimated total market share for PD-1 inhibitors (cemiplimab and pembrolizumab). No cost offsets for cemiplimab were presented.
MBS costs	\$118.30 ^b	MBS item number 13950	While the submission claimed that Q6W would decrease the use of this MBS item, it did not

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Data	Value	Source	Comment
			present any calculations or savings for the MBS.

Source: pp132-134 of the submission

AEMP, Approved ex-manufacturer price; DPMQ, Dispensed Price for Maximum Quantity; ECOG, Eastern Cooperative Oncology Group; laCSCC, locally advanced cutaneous squamous cell carcinoma; MBS, Medicare Benefits Schedule; mCSCC, metastatic cutaneous squamous cell carcinoma; mls, millilitres; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; NCCI national cancer control indicators; Q3W 3-weekly dosing schedule; Q6W 6-weekly dosing schedule; UK, United Kingdom; Yr, year

^a Based on July 2023 pricing calculator and weighted for public/private split (24.74/75.26%)

^b Updated to reflect current MBS item cost

6.54 The estimated use and financial estimates of the PBS/RPBS listing of pembrolizumab based on published prices are shown in Table 9.

Table 9: Estimated use and financial implications (published prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total treated patients	1	1	1	1	1	1
Total script numbers – initiating (PBS/RPBS)	2	2	2	2	2	3
Total script numbers - continuing (PBS/RPBS)	2	2	2	2	2	2
Cost PBS initiating	4	4	4	4	4	4
Cost PBS continuing	4	5	5	5	5	5
Less co-payment	6	6	6	6	6	6
Net cost PBS	7	7	7	7	7	8
Cost RPBS initiating	9	9	9	9	9	9
Cost RPBS continuing	9	10	10	10	10	10
Less co-payment	6	6	6	6	6	6
Net cost RPBS	10	11	11	11	11	11
Net cost PBS/RPBS	7	7	8	8	8	8
Net cost PBS/RPBS – cost minimised published price ^a	7	7	7	7	7	8

Source: Table 4-2.1, 4.3-4, p134, 137 of the submission with the DPMQ updated during the evaluation using the July 2023 pricing calculator (this update had minimal impact on the overall financial estimates)

MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; RPBS, repatriation Pharmaceutical Benefits Scheme

^a Using the cost-minimised price established in the economic analysis (AEMP \$3,645.00 per 100 mg) instead of the current published AEMP for pembrolizumab (\$3,824.00) for other PBS listed indications.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 10,000 to < 20,000

³ 20,000 to < 30,000

⁴ \$100 million to < \$200 million

⁵ \$200 million to < \$300 million

⁶ net cost saving

⁷ \$300 million to < \$400 million

⁸ \$400 million to < \$500 million

⁹ \$0 to < \$10 million

¹⁰ \$10 million to < \$20 million

¹¹ \$20 million to < \$30 million

6.55 The total cost to the PBS/RPBS of listing pembrolizumab based on the published price was estimated to be \$300 million to < \$400 million in Year 1 increasing to \$400 million to < \$500 million in Year 6, totalling >\$1 billion in the first 6 years of listing. The price applied for the financial estimates was the current published AEMP for pembrolizumab (\$3,824 per 100 mg) for other PBS listed indications rather than the cost-minimised price established in the economic analysis (\$3,645).

- 6.56 As outlined in paragraph 6.52, the submission revised two key parameters from the PBAC's March 2022 consideration for cemiplimab: the incidence of CSCC (from 0.7% to 0.777%) and the proportion of patients who develop laCSCC or mCSCC (from 1.67% in Year 1 in prevalent patients and 1.4% in Years 2 to 6 for incident patients for cemiplimab to 3.7% in Years 1 to 6 for pembrolizumab). The ESC noted these inputs resulted in a significantly higher estimate for the number of treated patients compared to the cemiplimab submission.
- 6.57 The incidence rate of CSCC used by the submission, 0.777%, was taken from a case-controlled study of reported CSCC (Wilson et al., 2022). It is unclear how generalisable these findings are to the wider Australian context (see Table 8). The financial estimates demonstrated sensitivity to this parameter (SA1 in Table 10), when a 0.7% incidence rate was applied, the estimated cost in Year 6 was \$300 million to < \$400 million and the total cost for the first 6 years of listing was >\$1 billion. The PSCR maintained that the incidence rate of 0.777% from Wilson et al. (2022) likely represents the midpoint estimate considering the variation due to latitudinal gradient across Australia. The PSCR further argued that the estimate from Wilson et al. (2022) is generalisable to the Australian population due to similarities in ethnographic and population characteristics between their population and the data from the non-melanoma Tasmanian registry (Raganini et al. 2021). The ESC recalled that in the consideration of cemiplimab for this indication, DUSC advised that the incidence from the NCCI national survey (Staples et al. 2006), although old, was likely to represent the best available evidence (Table 14, cemiplimab, PSD, March 2022 PBAC meeting).
- 6.58 The 3.7% of patients who develop laCSCC or mCSCC used by the submission came from a New Zealand study (Brougham et al., 2012). It was significantly higher than the 1.67% and 1.4% prevalence and incidence estimates used in the cemiplimab submission, which came from a UK study (Venables et al. 2018). The submission claimed that the Australian incidence of laCSCC and mCSCC may be higher than the UK incidence. This estimate is highly uncertain and has a significant impact on the financial estimates. When the 1.4% rate was applied the financial impact more than halved to \$100 million to < \$200 million in Year 6 and a total of \$900 million to < \$1 billion for the first 6 years (SA2 in Table 10). The multivariate sensitivity analysis conducted during the evaluation (Table 10) using inputs from the cemiplimab submission (CSCC incidence of 0.7% and proportion developing laCSCC or mCSCC of 1.4%) may better reflect the patient numbers presented in the cemiplimab submission. The PSCR argued that in the consideration of cemiplimab DUSC had considered that the incidence of late stage disease may be higher in Australia than in the UK. The ESC noted that the DUSC had identified studies that reported incidences of 1.2% to 3.7% and that the 1.67% and 1.4% prevalence and incidence estimates had been accepted by the PBAC in March 2022 (para 7.10, cemiplimab, PSD, March 2022 PBAC meeting).
- 6.59 The submission did not include grandfathered patients in the Year 1 total treated estimates. This was inconsistent with the requested restriction. The submission claimed that the grandfathered patients were considered minimal (< 500) and thus

were not included in the utilisation and cost model. The submission did not provide evidence to support this.

6.60 The submission assumed substitution of cemiplimab with pembrolizumab. However, the submission did not present cost offsets for cemiplimab.

6.61 Table 10 presents the sensitivity analysis presented in the submission and conducted during the evaluation.

Table 10: Sensitivity analyses for financial estimates (published prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case						
Total treated patients	1	1	1	1	1	1
Net cost to PBS/RPBS ^a (\$)	2	2	3	3	3	3
CSCC incidence (base case 0.777%)						
SA1: 0.7% from NCCI national survey						
Total treated patients	1	1	1	1	1	1
Net cost to PBS/RPBS(\$)	5	2	2	2	2	2
% of patients who develop laCSCC or mCSCC (base case 3.7%)						
SA2: 1.4% from Venables et al. 2018						
Total treated patients	1	1	1	1	1	1
Net cost to PBS/RPBS(\$)	4	4	4	4	4	4
SA3: 1.9% from Brougham et al. 2012						
Total treated patients	1	1	1	1	1	1
Net cost to PBS/RPBS(\$)	4	5	5	5	5	5
SA4: 2.1% from Robsahm et al. 2015						
Total treated patients	1	1	1	1	1	1
Net cost to PBS/RPBS(\$)	4	5	5	5	5	5
Multivariate analysis: 0.7% CSCC incidence (NCCI) & 1.4% proportion of participant who develop laCSCC or mCSCC (Venables)						
Total treated patients	1	1	1	1	1	1
Net cost to PBS/RPBS(\$)	4	4	4	4	4	4

Source: Table 4.6-1, p140 of the submission and conducted during the evaluation

CSCC, cutaneous squamous cell carcinoma; laCSCC locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; NCCI, National Cancer Control Indicators; PBS, Pharmaceutical Benefit Scheme; RPBS, Repatriation Pharmaceutical benefits Scheme; SA, sensitivity analysis; Q3W, every 3 weeks; Q6W, every 6 weeks.

^a Base case revised during the evaluation with updated DPMQ using the July 2023 pricing calculator.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² \$300 million to < \$400 million

³ \$400 million to < \$500 million

⁴ \$100 million to < \$200 million

⁵ \$200 million to < \$300 million

6.62 The PSCR argued that pembrolizumab may improve patient and carers capacity (particularly rural/regional) to present to hospital and maximise treatment adherence through its Q6W dosing. In addition, the PSCR argued that familiarity with the use of pembrolizumab would drive increased uptake, beyond that of cemiplimab. As such, the PSCR stated that the current utilisation of cemiplimab is unlikely to reflect the full eligible patient population. The ESC noted that both cemiplimab and pembrolizumab submissions assumed high uptake rates (see Table 8). The ESC noted that the revision of the assumptions around two key eligible patient parameters from the PBAC's March 2022 consideration for cemiplimab (see paragraph 6.56) resulted in significantly increased patient numbers and financial implications in this CMA based submission. The ESC noted the comparison between the base case and the multivariate sensitivity analysis provided in Table 10 indicated the financial impact of the resubmission base case is almost three times higher than that accepted by the PBAC in the March 2022 consideration of cemiplimab.

Quality Use of Medicines

6.63 The submission noted that to ensure the quality use of pembrolizumab the latest information will be provided to physicians, nurses, pharmacists, and patients about how to identify and manage potential treatment-related adverse events and immune-related adverse events. These materials will be provided through education programs aligned to major oncology clinician and nurse conferences and will include extensive peer support.

6.64 Clinicians and patients will have access to a 1800 medical information service. This service will include the development of comprehensive materials to ensure rapid and appropriate response to any enquiries.

Financial Management – Risk Sharing Arrangements

6.65 The submission stated that the sponsor would agree to collaborate with the Commonwealth to determine how best to ensure that the financial caps are reflective of the laCSCC and mCSCC burden of disease for pembrolizumab and cemiplimab.

6.66 The submission claimed that based on the strong uptake of cemiplimab in this population since it was listed in November 2022, the current financial caps may be underestimated. Cemiplimab is currently listed under a Risk Sharing Arrangement. In March 2022, the PBAC considered the use in patients with an ECOG PS of 2 was likely and that this risk should be managed with a Risk Sharing Arrangement. At that time, the PBAC advised that a Risk Sharing Arrangement with a 10% rebate for utilisation above the agreed estimates would be necessary to minimise the high risk of

cemiplimab use outside the proposed restriction (para 7.11, cemiplimab, PSD, March 2022 PBAC Meeting).

- 6.67 The PSCR noted that at the time of the November 2023 PBAC meeting, cemiplimab will have been listed for approximately 12 months and suggested the PBAC should re-evaluate whether the previously agreed financial caps suitably account for all laCSCC and mCSCC patients. The ESC considered that, as reported for cemiplimab in March 2022 (see paragraph 6.66), there was a high risk of use of pembrolizumab outside of the proposed restriction. The ESC considered this included the risk of use outside the proposed restriction in patients with borderline resectable disease. The ESC considered that the risk of use outside of the proposed restriction would likely be best managed within existing PBS risk sharing arrangements for this population. The ESC considered that with less than 1 full year of data for cemiplimab it was too early to address predicted versus actual use in terms of risk sharing arrangements. The pre-PBAC response reiterated the PSCR argument that the PBAC should re-evaluate whether the previously agreed financial caps suitably account for all laCSCC and mCSCC patients.

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 (EFC) Authority Required listing for pembrolizumab for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) that it not curable by surgery or radiation.
- 7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of pembrolizumab would be acceptable if it were cost-minimised against cemiplimab, and included in the current Risk Sharing Arrangement for CSCC with cemiplimab.
- 7.3 With regard to the requested listing and restriction, the PBAC advised that:
- An Authority Required (Telephone/Online PBS Authorities system) listing was appropriate to ensure consistency with ECOG performance status requirements and the proposed 24 month lifetime maximum of duration of therapy.
 - The number of repeats for initial therapy should be reduced to one for the 400 mg every 6 weeks dosing regimen and two for the 200 mg every 3 weeks dosing regimen (see paragraph 3.5).
 - The number of repeats for continuing therapy should be amended to three for the 400 mg every 6 weeks dosing regimen and seven for the 200 mg every 3 weeks dosing regimen (see paragraph 3.5).
 - Clinical criterion preventing the subsequent use of immunotherapy should be incorporated in cemiplimab and pembrolizumab listings (see paragraph 3.6).

- Administrative advice regarding the sponsor request for Special Pricing Arrangements should be included.
 - A grandfathering restriction was appropriate.
- 7.4 The PBAC recalled that in the March 2022 consideration of cemiplimab it had considered that there was a high unmet clinical need for treatment due to the symptom burden from locally advanced disease and poor quality of life associated with the disfiguring complications of the disease (para 7.3, cemiplimab, Public Summary Document (PSD), March 2022 PBAC meeting). The PBAC agreed with the ESC that the listing of cemiplimab reduced the high clinical need for treatment options. However, the PBAC noted the consumer comments from a health care professional and the Melanoma & Skin Cancer Advocacy Network which highlighted the need for additional treatment options. In addition, the PBAC noted the Medical Oncology Group of Australia's support for the submission.
- 7.5 The PBAC considered the nominated comparator of cemiplimab was reasonable.
- 7.6 The claim of non-inferior effectiveness and safety of pembrolizumab over cemiplimab was based on an unmatched, unanchored indirect comparison between four single arm studies (pembrolizumab: CARSKIN and KN629; cemiplimab: Study 1540 and Study 1423). The PBAC acknowledged the concerns raised by the ESC regarding differences in baseline characteristics across the studies (see paragraph 6.13) and noted the submission argument that a matched adjusted indirect comparison was not appropriate (see paragraph 6.20). The PBAC also acknowledged the differences between the included studies in the definitions used for locally advanced cutaneous squamous cell carcinoma (laCSCC) and metastatic cutaneous squamous cell carcinoma (mCSCC) cohorts and the duration of follow-up (see paragraph 6.33). The PBAC recalled that Study 1540 (Group 1-3) and Study 1423 were considered by the PBAC for cemiplimab in March 2022. The PBAC noted the objective response rate (ORR) reported for the total populations of pembrolizumab studies (42% in CARSKIN and 40.3% in KN629) passed their respective study clinically meaningful thresholds but were numerically lower compared to the ORRs reported in Study 1540 (47.2% in Group 1-3 and 45.1% in Group 6 in Study 1540) and Study 1423 (50%). The PBAC noted the submission argument that the differences between studies bias in favour of cemiplimab due to pembrolizumab having a prognostically poorer patient population overall. The PBAC agreed with the ESC that the direction and magnitude of the impact of the differences in baseline characteristics on outcome results was unknown. Overall, the PBAC considered that the clinical claim of non-inferior efficacy was uncertain but likely reasonable.
- 7.7 The PBAC considered that the claim of non-inferior comparative safety was uncertain but likely reasonable.
- 7.8 The submission presented a cost-minimisation approach (CMA) versus cemiplimab. The PBAC noted concerns regarding uncertainty in the estimating of equi-effective doses due to the different durations of follow-up and treatment exposure across the

studies. In addition, the PBAC noted that study KN629 and Study 1540 are ongoing and therefore data on these parameters is incomplete. While the CMA draws from a limited clinical evidence base, the PBAC agreed with the ESC that the evidence available indicated the financial risk to the Government of the treatment duration for pembrolizumab being longer than cemiplimab was low. The PBAC considered the following equi-effective doses appropriate:

- pembrolizumab 200 mg every 3 weeks (Q3W) is equivalent to cemiplimab 350 mg Q3W, and
- pembrolizumab 400 mg every 6 weeks is equivalent to 2x cemiplimab 350 mg Q3W.

7.9 The PBAC noted the submission revised two key parameters of the financial estimates compared to the March 2022 consideration for cemiplimab. These were: incidence of CSCC (from 0.7% to 0.777%) and the proportion of patients who develop laCSCC or mCSCC (from 1.67% in Year 1 in prevalent patients and 1.4% in Years 1 to 6 for incident patients for cemiplimab to 3.7% in Years 1 to 6 for pembrolizumab). The PBAC noted that the revised key parameters resulted in significantly increased patient numbers and financial implications (see paragraph 6.62) in this cost-minimisation based submission. The PBAC recalled that in March 2022 it had been explicit in accepting the cemiplimab estimates as an appropriate basis for a Risk Sharing Arrangement with a 1% rebate (para 7.10 and 7.11, cemiplimab, PSD, March 2022 PBAC meeting). As such, the PBAC did not accept the revised inputs for the incidence of CSCC and the proportion of patients who develop laCSCC or mCSCC proposed by the submission. The PBAC advised that these inputs should revert to those used in the March 2022 cemiplimab submission and that that for the financial estimates it was reasonable to assume an equal treatment duration for pembrolizumab and cemiplimab. The PBAC considered that applying these assumptions would result in the listing being cost neutral. The PBAC noted the submissions did not include grandfathered patients (assumed to be < 500 patients) in the Year 1 total treated estimates and considered that this was appropriate as they would already be accounted for in the estimates used to determine current risk sharing arrangements.

7.10 The PBAC recalled that in March 2022 a Risk Sharing Arrangement with a 1% rebate was considered necessary to minimise the high risk of use of cemiplimab outside the proposed restriction (para 7.11, cemiplimab, PSD, March 2022 PBAC meeting). The PBAC noted the Pre-Sub-Committee and pre-PBAC response requests for the PBAC to re-evaluate whether the previously agreed financial caps suitably account for all laCSCC and mCSCC patients. The PBAC recalled that in the March 2022 consideration of cemiplimab it had accepted measures to address a highly uncertain incremental cost-effectiveness ratio in an area of high unmet clinical need and recommended a Risk Sharing Arrangement with a 1% rebate (para 7.9 and 7.11, cemiplimab, PSD, March 2022 PBAC meeting). The PBAC considered the listing of cemiplimab reduced the high clinical need for treatment options. The PBAC

considered that requests for use beyond the financial estimates previously agreed by the Committee for cemiplimab would require further exploration of cost-effectiveness implications and noted that this was not undertaken for this submission. The PBAC advised that pembrolizumab be included in the current Risk Sharing Arrangement for cemiplimab for the treatment of laCSCC or mCSCC that it not curable by surgery or radiation. The PBAC advised that the existing Risk Sharing Arrangement remains appropriate to minimise the high risk of use outside of the proposed restriction.

- 7.11 The PBAC noted the flow-on restriction amendments for cemiplimab (PBS item codes 13125F and 13135H) outlined in paragraph 8.2.
- 7.12 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because pembrolizumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over cemiplimab, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add indication to an existing medicinal product pack (pembrolizumab 100 mg/4 ml injection, 4 ml vial) as follows:

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
PEMBROLIZUMAB Injection	NEW 1 (Public) MP	400 mg	1
	NEW 2 (Private) MP		
Available brands			
Keytruda (pembrolizumab 100 mg/4 ml injection, 4 ml vial)			

Restriction Summary/Authority Required (currently attached to cemiplimab) Restriction Summary New 1 / ToC: New 1.1: Authority Required	
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Level / Method:

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	<input checked="" type="checkbox"/> Authority Required – Telephone/Online PBS Authorities system
	Administrative Advice: No increase in the maximum amount or number of units may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Indication: Metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC)
	Treatment Phase: Initial treatment covering the first 2 treatment cycles
	Clinical criteria: The condition must be unsuitable for each of: (i) curative surgical resection, (ii) curative radiotherapy
	AND
	Clinical criteria: Patient must have had a WHO performance status of 0 or 1
	AND
	Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria: Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition; or
	Patient must have experienced a severe intolerance to the above therapy leading to permanent treatment discontinuation.
	Administrative Advice: An additional 1 repeat prescription (2 in total) may be sought where the dosing is 200 mg once every 3 weeks (this treatment phase then covers the first 3 treatment cycles).

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	№.of Rpts
PEMBROLIZUMAB Injection	NEW 3 (Public) MP NEW 4 (Private) MP	400 mg	3
Available brands			
Keytruda (pembrolizumab 100 mg/4 ml injection, 4 ml vial)			
Restriction Summary 1 (currently attached to cemiplimab): Authority Required			
Restriction Summary New 2 / ToC: New 2.1: Authority Required			
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners		
	Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/Online PBS Authorities system		
	Administrative Advice: No increase in the maximum amount or number of units may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		
	Administrative Advice:		

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	Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Indication: Metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC)
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised therapy with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	Treatment criteria:
	Patient must not be undergoing treatment with this drug as a PBS benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 months from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs
	Administrative Advice:
	An additional 4 repeat prescriptions (7 in total) may be sought where the dosing is 200 mg once every 3 weeks.
Restriction Summary / Authority Required (currently attached to cemiplimab)	
Restriction Summary New 3 / ToC: New 3.1: Authority Required	
	Indication: Metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC)
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements
	Clinical criteria:
	Patient must have received non-PBS-subsidised therapy treatment with this drug for this condition prior to <i>[insert listing date here]</i>
	AND
	Clinical criteria:
	The condition must be unsuitable for each of: (i) curative surgical resection, (ii) curative radiotherapy
	AND
	Clinical criteria:
	Patient must have had a WHO performance status of 0 or 1 prior to initiation of non-PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	Patient must not have received prior treatment with a programmed cell death-1/ligand-1 (PD-1/PD-L1) inhibitor for this condition at the time non-PBS subsidised supply of this drug commenced; or
	Patient must have experienced a severe intolerance requiring treatment discontinuation to a PD-1/PDL-1 inhibitor therapy other than this one for the stated indication, prior to the non-PBS subsidised supply of this drug
	Treatment criteria:
	Patient must not be undergoing treatment with this drug as a PBS benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24

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	months from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled'; where this occurs
	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 'Continuing treatment' criteria.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice: An additional 4 repeat prescriptions (7 in total) may be sought where the dosing is 200 mg once every 3 weeks.

Flow on changes:

8.2 Amend the following cemiplimab listings as follows:

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
CEMIPLIMAB Injection	13152F (Public)	350 mg	2
	MP 13135H (Private) MP		
Available brands			
Libtayo (cemiplimab 350 mg/7 ml injection, 7 ml vial)			

Edit Restriction Summary / Authority Required	
	Caution: In the first few months after starting immunotherapy, a transient tumour flare may occur that may be mistaken as disease progression despite an overall positive response to treatment.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Indication: Metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC)
	Treatment Phase: Initial treatment covering the first 3 treatment cycles
	Clinical criteria: The condition must be unsuitable for each of: (i) curative surgical resection, (ii) curative radiotherapy
	AND
	Clinical criteria: Patient must have had a WHO performance status of 0 or 1
	AND
	Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria: Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition; or

	<i>Patient must have experienced a severe intolerance to the above therapy leading to permanent treatment discontinuation.</i>
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This restriction 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

The sponsor had no comment.