6.06 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] Program) Authority Required (STREAMLINED) listing for pembrolizumab for the perioperative treatment of patients with resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC). The proposed use includes neoadjuvant treatment (prior to surgical resection), followed by adjuvant treatment (after surgical resection) in combination with radiotherapy, with or without chemotherapy, and subsequently as monotherapy (PEM+SoC).

1.2 Listing was requested based on a cost-effectiveness analysis versus standard of care (SoC) comprising adjuvant radiotherapy with or without chemotherapy.

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

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

Component	Description
Population	Resectable locally advanced head and neck squamous cell carcinoma
Intervention	2 cycles of 200 mg pembrolizumab IV Q3W (or equivalent[a]) prior to surgical resection followed by 3 cycles of 200 mg pembrolizumab IV Q3W (or equivalent[a]) in combination with SoC, followed by 12 cycles of 200 mg pembrolizumab IV Q3W (or equivalent[a])
Comparator	SoC (radiotherapy +/- chemotherapy administered in the adjuvant setting)
Outcomes	Primary outcomes: EFS per RECIST 1.1 as assessed by BICR Secondary outcomes: OS, mPR and pCR by BIPR, HRQoL, and AEs
Clinical claim	In resectable locally advanced head and neck squamous cell carcinoma, PEM+SoC is superior with respect to efficacy and has an inferior but manageable safety profile when compared to SoC alone.

Source: Table 1.1-1, p6 of the submission.

AEs = adverse events; BICR = blinded independent central review; BIPR = blinded independent pathologist review; EFS = event-free survival; HRQoL = health-related quality of life; IV = intravenous; mPR = major pathological response; OS = overall survival; pCR = pathological complete response; PEM = pembrolizumab; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST = Response Evaluation Criteria in Solid Tumours; SoC = standard of care

[a] Refers to the pembrolizumab 400 mg Q6W regimen

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. The proposed TGA indication was:

For the treatment of patients with resectable locally advanced HNSCC as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without platinum-containing chemotherapy and then as monotherapy.

2.2 At the time of PBAC consideration, the Delegate's Overview was available. The TGA Delegate was inclined to approve pembrolizumab for the treatment of adult patients with resectable locally advanced HNSCC whose tumours express programmed cell death ligand 1 (PD-L1) with a combined positive score (CPS) ≥1, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent. The Delegate requested ACM advice on whether the proposed indication should be limited to patients whose tumours express PD-L1 with a CPS ≥1 and whether cisplatin should be specified, rather than platinum-containing chemotherapy.

2.3 The Delegate proposed to impose a condition of registration to provide the results of interim analysis 2 (IA2) and the final analysis for KEYNOTE-689 (KN689) as a category 1 application when available.

Previous PBAC consideration

2.4 The PBAC has not previously considered pembrolizumab for the treatment of LA HNSCC. However, at the March 2022 PBAC meeting, the PBAC recommended the listing of pembrolizumab for the treatment of patients with recurrent or metastatic HNSCC.

3 Requested listing

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

MEDICINAL PRODUCT **Form**	**Dispensed Price Max Amt**	**Max. Amount**	**№.of Rpts**
~~PEMBROLIZUMAB~~ ~~Solution concentration for I.V. infusion~~	~~Published prices:~~ ~~$7,738.73 (Public)~~ ~~$7,891.47 (Private)~~ ~~Effective prices:~~ ~~$[redacted] (Public)~~ ~~$[redacted] (Private)~~	~~200 mg~~	~~7~~
PEMBROLIZUMAB Solution concentration for I.V. infusion	Published prices: $15,386.23 (Public) $15,646.02 (Private) Effective prices: $[redacted] (Public) $[redacted] (Private)	400 mg	~~3~~ 7
Available brands			
Keytruda (pembrolizumab 100 mg in 4mL solution concentration for I.V. infusion, 1 vial)			

Source: Table 1.4-1, p20 of the submission.
I.V. = intravenous

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Severity: Resectable locally advanced
Condition: Squamous cell carcinoma of the oral cavity, pharynx or larynx
Indication: Resectable locally advanced squamous cell carcinoma of the oral cavity, pharynx or larynx
Clinical criteria:
Patient must have stage III-IVB squamous cell carcinoma of the oral cavity, pharynx or larynx
AND
Clinical criteria:
Patient must have tumour(s) that are resectable as assessed by the treating clinician
OR
Patient must have undergone surgical resection
AND
Clinical criteria:
Patient must have a WHO performance status of 1 or less
AND
Clinical criteria:
Patient must not have experienced disease recurrence or progression while being treated with this drug for this condition
AND
~~**Clinical criteria:**~~
~~Patient must not have received prior PBS subsidised treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for squamous cell carcinoma of the oral cavity, pharynx or larynx~~
Treatment criteria:
The treatment must be commenced as neoadjuvant therapy and continued in combination with radiation therapy +/- chemotherapy *after surgical resection*~~, followed by pembrolizumab monotherapy as maintenance~~
OR
The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition
AND
Treatment criteria:
~~Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS-subsidised therapy~~ *The treatment must not exceed a total of 12 cumulative months, either as (i) 17 doses (based on a 3-weekly dose regimen), (ii) 8 doses (based on a 6-weekly dose regimen) whichever comes first from the first dose of this drug regardless of if it was PBS/non-PBS subsidised*
AND
Treatment criteria:
Patient must be undergoing treatment with this drug administered once every 3 weeks at 200mg - prescribe up to 7 repeat prescriptions; OR Patient must be undergoing treatment with this drug administered once every 6 weeks at 400mg - prescribe up to 3 repeat prescriptions

Administrative Advice: No increase in the maximum quantity or number of units may be authorised AND No increase in the maximum number of repeats may be authorised AND Special Pricing Arrangements apply ~~AND~~ ~~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~~

Source: Table in p22 of the submission.

3.2 The submission requested a Special Pricing Arrangement (SPA) for pembrolizumab as perioperative treatment for LA HNSCC. The submission proposed an effective ex-manufacturer price of $[redacted] per 100 mg vial and the pre-PBAC response reduced this to $[redacted] per 100 mL vial.

3.3 The submission proposed a single restriction for both neoadjuvant and adjuvant treatment, with a limit on the total treatment duration and a requirement for patients to discontinue treatment upon disease recurrence or progression. This is consistent with the recent listing of pembrolizumab as perioperative therapy for early-stage triple-negative breast cancer (TNBC). The maximum treatment duration (12 months) specified in the requested PBS listing is in line with the duration of the intervention in the key clinical trial (KEYNOTE-689), hereafter referred to as KN689.

3.4 A separate grandfathering listing was not requested. The submission stated that the treatment criteria in the proposed PBS restriction allow grandfathered patients who have received non-PBS subsidised pembrolizumab to access PBS treatment. The evaluation considered that the proposal of one treatment agnostic restriction was reasonable. The Secretariat noted the restriction required further amendment to accommodate grandfathering patients. Suggested amendments are shown above.

3.5 The submission proposed that a 'Patient must not have received prior PBS subsidised treatment with a programmed cell death-1 (PD-1) inhibitor or a PD-L1 inhibitor for squamous cell carcinoma of the oral cavity, pharynx or larynx'. This was likely to align with previous advice from the PBAC requiring a once-in-a-lifetime restriction in the context of PD-L1 inhibitors limiting its use in the later line settings. However, there are no available PD-L1 inhibitors in any earlier line of therapy for squamous cell carcinoma of the oral cavity, pharynx or larynx, and therefore this criterion may be redundant.

3.6 The requested PBS listing for patients with resectable locally advanced squamous cell carcinoma of the oral cavity, pharynx or larynx is narrower than the proposed TGA indication, which is for resectable LA HNSCC regardless of site of disease. The PBAC agreed with the evaluation that the exclusion of tumours in the nasopharyngeal, sinus, or other para-nasal regions from the proposed PBS target population was appropriate and consistent with the exclusion criteria of KN689, and with the current pembrolizumab listing for recurrent or metastatic HNSCC.

3.7 The proposed PBS restriction permits use of perioperative pembrolizumab in patients with Stage IVB disease; whereas these patients were excluded from the key trial. Stage

IVB HNSCC is generally deemed unresectable; only a small proportion could be considered for resection. The submission stated that Stage IVB patients were included in the proposed population due to these patients being overrepresented in marginalised groups (i.e. First Nations people) and excluding them from treatment may cause equity issues. Disease stage (III vs. IVA) was one of the stratification factors in KN689. Subgroup results showed a more pronounced event-free survival (EFS) benefit from pembrolizumab in patient with less advanced Stage III disease (N=183) (hazard ratio [HR]: 0.42; 95% confidence interval [CI]: 0.25, 0.71) compared with the Stage IVA subgroup (N=528) (HR: 0.85; 95% CI: 0.66, 1.10). As the 95% CIs only overlapped slightly, a treatment effect variation associated with pembrolizumab across disease stage subgroups cannot be ruled out. The benefit/harm balance of the addition of perioperative pembrolizumab to adjuvant radiotherapy ± chemotherapy for the treatment of resectable Stage IVB disease is uncertain. The ESC considered the inclusion of Stage IVB patients in the proposed restriction was likely reasonable and noted that this stage of disease can be curative if disease is considered resectable. The PBAC agreed with the ESC and considered the inclusion of Stage IVB patients in the proposed restriction was reasonable.

3.8 The ESC noted that the clinical criterion 'Patient must have tumour(s) that are resectable as assessed by the treating clinician' was likely reasonable, though difficult to enforce in practice compared to the controlled conditions of the clinical trial. The PBAC agreed with the ESC and considered that this criterion could lead to some use in unresectable locally advanced patients. Additionally, the PBAC considered some patients with resectable locally advanced disease were likely to be accessing immunotherapy under the current listing for unresectable metastatic disease.

3.9 The proposed PBS target population has not been restricted to patients expressing PD-L1 because of the high prevalence of PD-L1 expression in LA HNSCC (PD-L1 CPS ≥ 1 accounting for 95.5% of the trial population in KN689) and the positive efficacy results in the overall trial patients. The PBAC has previously considered PD-L1 status in the context of recurrent and metastatic HNSCC. The PBAC previously considered that, based on the results of the KN048 trial, it was not possible to conclude that patients with CPS < 1 derive no benefit from pembrolizumab plus chemotherapy. A statistically significant survival benefit was observed in the unselected population treated with pembrolizumab plus chemotherapy at the interim analysis, final analysis and at 4-years follow-up. The PBAC previously advised that, on this basis, it was preferable that listing of pembrolizumab in combination with chemotherapy not exclude patients with CPS < 1 (paragraph 7.1, pembrolizumab public summary document [PSD], November 2021 PBAC meeting with March 2022 Addendum). In line with previous decisions, the PBAC advised that it remains appropriate not to restrict treatment to patients expressing PD-L1.

3.10 The PBAC considered that a flow-on change may be required to the current pembrolizumab and nivolumab listings for recurrent/metastatic HNSCC to preclude retreatment with a PD-1 inhibitor, in line with the "once per lifetime" rule for the majority of immunotherapies subsidised through the PBS.

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

4 Population and disease

4.1 Head and neck cancers encompass a range of malignancies, including in the oral cavity, larynx, oropharynx, and hypopharynx. In 2024, it was estimated that 5,531 new cases of head and neck cancer (including lip) were diagnosed in Australia, with the majority (~85%) of the cancers originating from the oral cavity, pharynx and larynx.[1] Squamous cell carcinoma (SCC) is the most common histology, accounting for approximately 93% of head and neck cancers.[2]

4.2 The submission noted that locally advanced disease is usually considered to be Stages III to IVB, as defined by the 8th Edition of the American Joint Committee on Cancer (AJCC) Tumour-Node-Metastasis (TNM) staging system. More than half (54−73%) of HNSCCs are diagnosed in the locally advanced setting.[2,3] LA HNSCC is aggressive and has a recurrence rate of 50% to 60%,[4] necessitating intensive treatment comprising surgery, radiotherapy, and systemic therapy.

4.3 The population proposed in the submission were patients with resectable LA SCC of the oral cavity, pharynx or larynx. In current clinical practice, the proposed PBS patients are often treated with definitive radiotherapy ± chemotherapy, given post-operatively. If relapse occurs, patients are assessed for eligibility for retreatment with local therapy. Patients whose disease cannot be managed with local therapy receive nivolumab or pembrolizumab ± chemotherapy, subject to line of therapy and time of recurrence.[5] Chemotherapy is given alone if patients are not eligible for, or contraindicated to, immunotherapy.

4.4 Pembrolizumab is a high affinity antibody against PD-1. It is an immune-checkpoint inhibitor that limits the activity of T lymphocytes in peripheral tissues. Pembrolizumab is proposed to be used as neoadjuvant therapy, followed by surgery, and then pembrolizumab treatment continues, in combination with radiotherapy ± chemotherapy (SoC) in the adjuvant setting and then as a single agent.

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

[1] Australian Institute of Health and Welfare (AIHW). Cancer summary data visualisation. AIHW. 2024; Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/summary-dashboard. [Accessed 25 July 2025].
[2] Foley J, Wishart LR, et al. Exploring the impact of remoteness on people with head and neck cancer: Utilisation of a state-wide dataset. *Aust J Rural Health*. 2023;31(4):726-43
[3] Kwok MMK, Wong A, Prasad J. Factors affecting timeliness in management of head and neck cancer. *ANZ J Surg*. 2023;93(10):2388-93.
[4] Black CM, Hanna GJ, *et al*. Real-world treatment patterns and outcomes among individuals receiving first-line pembrolizumab therapy for recurrent/metastatic head and neck squamous cell carcinoma. *Front Oncol*. 2023;13:1160144
[5] Pembrolizumab ± chemotherapy as first-line therapy in the recurrent/metastatic setting when disease recurs beyond 6 months of completion of systemic therapy if previously treated in the locally advanced setting *versus* nivolumab when disease progresses within 6 months of prior platinum-based chemotherapy.

5 Comparator

5.1 The submission nominated SoC, defined as adjuvant radiotherapy with or without chemotherapy, as the main comparator. The submission indicated that this definition of SoC for the treatment of resectable LA HNSCC in current Australian clinical practice was validated by the sponsor's clinical advisory board and is aligned with local and international guidelines.[6,7] The ESC considered that adjuvant radiotherapy ± chemotherapy was an appropriate comparator for pembrolizumab in the resectable locally advanced setting.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (8) and organisations (3) via the Consumer Comments facility on the PBS website.

6.3 The PBAC noted the advice received from Head and Neck Cancer Australia and Rare Cancers Australia supporting the PBS listing of pembrolizumab for the perioperative treatment of patients with resectable LA HNSCC. The organisations highlighted that surgical resection and radiation can often lead to serious complications, including severe disfigurement, loss of vision, and impairments in the ability to swallow, speak, eat, or drink, profoundly affecting both the physical and mental wellbeing of patients. Rare Cancers Australia noted that further treatment options may help to reduce the invasiveness of current procedures, ultimately enhancing patients' quality of life.

6.4 The PBAC noted comments from health care professionals supporting the PBS listing of pembrolizumab for the treatment of resectable LA HNSCC. The input emphasised that there is a critical unmet clinical need for these patients, noting that current SoC is associated with severe complications and poor clinical outcomes, where patients experience a high risk of recurrence within one year of surgery and poor 5-year overall survival. The health care professionals noted the improvement in EFS, and pathological response reported for pembrolizumab compared with SoC alone in the KN689 trial. The health care professionals considered these results clinically meaningful and would likely result in a greater likelihood of long-term remission, overall survival gains and improved quality of life. The input noted that, for patients and their families, the potential to reduce recurrence, extend survival, and minimise

[6] eviQ. Head and neck. Cancer Institute NSW. 2025; Available from: https://www.eviq.org.au/medical-oncology/head-and-neck. [Accessed 30 July 2025].
[7] National Comprehensive Cancer Network (NCCN). NCCN Guidelines Version 4.2025: Head and Neck Cancers. 2025.

treatment-related morbidity would lead to meaningful improvements in physical health, emotional wellbeing, and psychosocial functioning. The health care professionals noted the favourable clinical outcomes observed in patients receiving pembrolizumab in the metastatic setting and proposed that its earlier introduction in the treatment algorithm would offer therapeutic benefit and improve overall disease management. Health care professionals also noted a preference for the PBS listing to be flexible across PD-L1 strata, clinical staging (including IVB patients), and cisplatin eligibility. Health care professionals discussed the possible disadvantages of perioperative treatment with pembrolizumab, including toxicity and a potential for a delay in surgery. It was noted that some patients may experience disease progression during the neoadjuvant phase which would preclude surgery and may result in poorer health outcomes than if surgery had been performed earlier and highlighted the importance of carefully selecting patients with a low risk of rapid disease progression.

6.5 Individuals with HNSCC discussed medical complications experienced post-surgery. The individuals indicated a preference to receive pembrolizumab and considered it could reduce the risk of recurrence.

6.6 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the pembrolizumab submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the KEYNOTE-689 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab the highest grade 'A', categorising it as a treatment with substantial benefit in the curative setting.[8]

Clinical trials

6.7 The submission was based on one head-to-head trial (KN689) which compared PEM+SoC with SoC in patients with resectable Stage III-IVA SCC of the oral cavity, pharynx or larynx (N = 714).

6.8 Details of the KN689 trial presented in the submission are provided in Table 2.

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

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
KN689	Clinical Study Report A phase III, randomized, open-label study to evaluate pembrolizumab as neoadjuvant therapy and in combination with standard of care as adjuvant therapy for stage III-IVA resectable locoregionally advanced head and neck squamous cell carcinoma (LA HNSCC).	9th December 2024
	Publication Uppaluri, R., Haddad RI, et al. Neoadjuvant and adjuvant pembrolizumab in locally advanced head and neck cancer.	*N Engl J Med* 2025; 393(1): 37-50.
	Abstracts Uppaluri R, Haddad RI, et al. Neoadjuvant and adjuvant pembrolizumab plus standard of care in resectable locally advanced head and neck squamous cell carcinoma: phase 3 KEYNOTE 689 study. Abstract CT001	AACR Annual Meeting 2025. *Cancers Res* 2025; 85(8_Suppl 2)
	Adkins D, Haddad RI, et al. Neoadjuvant and adjuvant pembrolizumab plus standard of care in resectable locally advanced head and neck squamous cell carcinoma: exploratory efficacy analyses of the phase 3 KEYNOTE-689 study. Abstract 6012.	ASCO Annual Meeting 2025. *J Clin Oncol* 2025; 43(16_Suppl)

Source: Table 2.2-1, p29 of the submission.
AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology

6.9 The key features of the KN689 trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
PEM+SoC vs. SoC						
KN689	714	R, OL 27.1 mths	Varied depending on the subjectivity of the outcome[a]	Patients with resectable Stage III-IVA SCC of the oral cavity, pharynx or larynx	Primary: EFS by BICR Secondary: OS, mPR and pCR by BIPR, HRQoL, and AEs	KN689 patient level data applied.

Source: Information provided in Section 2.3, pp31−43 of the submission.
AEs = adverse events; BICR = blinded independent central review; BIPR = blinded independent pathologist review; EFS = event-free survival; HRQoL = health-related quality of life; mPR = major pathological response; OL = open-label; OS = overall survival; pCR = pathological complete response; PEM = pembrolizumab; R = randomised; SCC = squamous cell carcinoma; SoC = standard of care
[a] Low-to-moderate risk of bias for assessment of EFS, OS, mPR and pCR. Moderate-to-high risk of bias for assessment of patient-reported outcomes and AE outcomes.

6.10 KN689 has an open-label trial design. The ESC noted that the number of patients who were randomised but did not receive the study intervention or in-study surgery was higher in the SoC arm compared with the PEM+SoC arm (35 [10.0%] vs. 3 [0.8%]), but the reasons for not receiving treatment were not provided. The ESC agreed with the evaluation and considered that it is feasible that patients withdrew when they realised they were not receiving the study drug. It is not possible to determine whether patients who were randomised to the SoC arm but did not receive treatment had a better or worse prognosis, compared with treated patients. Nevertheless, the ESC considered that the imbalanced early dropout rate suggests underlying systemic bias.

6.11 The potential for bias from assessments for the primary endpoint, i.e. EFS[9], and key secondary outcomes of major pathological response (mPR)[10] and pathological complete response (pCR)[11], was likely reduced to some extent by using a blinded independent central review (BICR) in assessing images for efficacy measures and a blinded independent pathologist review (BIPR) in assessing pathological responses. However, the assessment of subjective health-related quality of life (HRQoL) and safety outcomes remains affected by a moderate to high risk of bias.

6.12 KN689 is an ongoing trial. The results presented in the submission were from the interim analysis 1 (IA1). As specified in the study protocol, the efficacy outcomes were evaluated and tested sequentially in patients with PD-L1 CPS ≥ 10, in patients with CPS ≥ 1, and in all-comers, i.e. the intention-to-treat (ITT) population.

6.13 At the data cutoff (DCO) of IA1, 69 patients in the PEM+SoC arm and 95 patients in the SoC arm experienced disease recurrence as their first EFS event (Table 4). Using these disease recurrence events as the denominator and the number of patients who subsequently received systemic therapies as the numerator, the proportion of patients who subsequently received immunotherapy post-recurrence was 18.9% (13/69) and 50.5% (48/95) in the PEM+SoC group and the SoC group, respectively. The ESC noted that in Australian clinical practice, the proportion of patients receiving immunotherapy post-recurrence following SoC would be much higher, given PBS reimbursement and treatment guidelines recommend the use of PD-L1 as SoC in this setting (see paragraph 6.36 for further discussion). Additionally, immunotherapy re-treatment received by 18.9% of patients post-recurrence in the PEM+SoC arm was not in line with the "one per lifetime" rule for most immunotherapies currently subsidised through the PBS. However, the ESC considered that the clinical benefit gained from re-treatment would likely be small. Overall, the ESC agreed with the evaluation that the OS benefit observed in KN689 may not accurately reflect outcomes that would occur in Australian clinical practice, where the benefit of PEM+SoC vs SoC would likely be lower.

6.14 The key trial only included one pembrolizumab treatment arm. The design of the trial did not allow for isolating the contributions of each of the two lines of pembrolizumab treatment, i.e. neoadjuvant as monotherapy and adjuvant in combination with SoC. Therefore, it is not possible to determine the benefit/harm trade-off for each individual line of therapy. During the evaluation, clinical trials were identified which investigated the use of pembrolizumab for LA HNSCC as neoadjuvant therapy in combination with chemotherapy (EFFECT-neo study, NCT06102395[12]) or as adjuvant therapy in combination with radiotherapy and cisplatin (ADRISK study,

[9] EFS is defined as time from the date of randomisation to the date of first record of any of the following events: radiographic disease progression, radiographic disease progression during the neoadjuvant phase that precludes surgery, local or distant disease progression or recurrence as assessed with imaging or biopsy as indicated, death due to any cause.

[10] mPR is defined as having ≤10% invasive squamous cell carcinoma within the resected primary tumour specimen and all sampled regional lymph nodes

[11] pCR is defined as having no residual invasive squamous cell carcinoma within the resected primary tumour specimen and all sampled regional lymph nodes

[12] https://clinicaltrials.gov/study/NCT06102395

NCT03480672[13]). However, at the time of evaluation the neoadjuvant pembrolizumab trial was still recruiting participants; and the adjuvant pembrolizumab trial completed in January 2025 but results had not yet been published. The ESC noted and agreed with the Pre-sub Committee Response (PSCR) that the trial results from KN689 likely suggest a clinical benefit associated with neoadjuvant pembrolizumab, given that fewer patients had high-risk pathological features after surgery in the PEM+SoC arm compared to the SoC arm, which enabled patients in the PEM+SoC arm to receive less intensive SoC and experience less adverse events associated with chemotherapy and radiotherapy (see paragraphs 6.23 and 6.28).

Comparative effectiveness

6.15 Results are presented in Table 4 of the primary endpoint of EFS by BICR as per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) in the ITT population of KN689. The EFS Kaplan-Meier (KM) curves are presented in Figure 1.

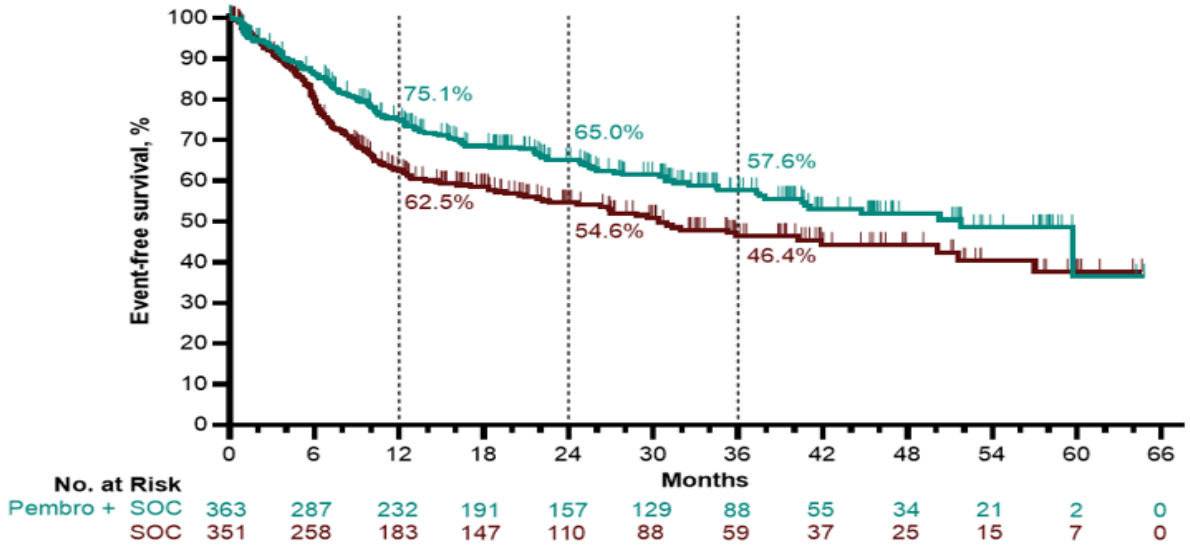
Table 4: Results of EFS by BICR in the KN689 trial (ITT population)

	PEM+SoC N=363	SoC N=351
Number of events (%)	136 (37.5)	159 (45.3)
Death	67 (18.5)	64 (18.2)
Distant progressive disease	26 (7.2)	51 (14.5)
Local and distant progressive disease	4 (1.1)	7 (2.0)
Local progressive disease/recurrence	39 (10.7)	37 (10.5)
Kaplan-Meier estimates (months)[a]		
Median (95% CI)	51.8 (37.5, NR)	30.4 (21.8, 50.1)
HR (95% CI)[b]	**0.73 (0.58, 0.92)**	
p-value[c]	**0.00411**	
EFS rate, % (95% CI)		
At month 12	75.1 (70.0, 79.4)	62.5 (56.9, 67.5)
At month 24	65.0 (59.4, 70.1)	54.6 (48.7, 60.1)
At month 36	57.6 (51.5, 63.3)	46.4 (40.0, 52.5)
At month 48	52.0 (45.1, 58.4)	44.2 (37.5, 50.8)

Source: Table 2.5-1, p69 of the submission
BICR = blinded independent central review; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; ITT = intention-to-treat; NR = not reached; PEM = pembrolizumab; SoC = standard of care; sSAP = supplementary statistical analysis plan
Data cutoff: 25 July 2024
Statistically significant differences are **bolded**
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

[13] https://clinicaltrials.gov/study/NCT03480672

Figure 1: Kaplan-Meier plot of EFS by BICR in the KN689 trial (ITT population)



Source: Figure 2.5-1, p70 of the submission
BICR = blinded independent central review; EFS = event-free survival; ITT = intention-to-treat; Pembro = pembrolizumab; SOC = standard of care
Data cutoff: 25 July 2024

6.16 Based on results from the pre-specified IA1, perioperative pembrolizumab in combination with adjuvant SoC was associated with a statistically significant improvement in EFS assessed by BICR, compared with SoC, with a gain of 21.4 months in median EFS (51.8 months vs. 30.4 months; HR: 0.73; 95% CI: 0.58, 0.92; p-value: 0.00411). The EFS KM curve for the PEM+SoC group separated from the SoC group curve at approximately Month 3 and remained separated through to approximately Month 57, at which time point the trial data became unreliable due to the low number of patients at risk.

6.17 There were 136 (37.5%) patients that experienced an EFS event in the PEM+SoC arm, compared with 159 (45.3%) patients in the SoC arm. The ESC noted that the difference was primarily attributable to the lower number of instances of distant progressive disease as the first EFS event in the PEM+SoC group (26 [7.2%] vs. 51 [14.5%]). The ESC considered that this was a clinically meaningful outcome, as distant recurrences are often incurable.

6.18 Death was the most commonly reported first EFS failure event in both treatment groups (67 [18.5%] vs. 64 [18.2%]).

6.19 The analyses of EFS based on BICR assessment in patients with PD-L1 CPS ≥10 and CPS ≥1 were pre-specified in the trial protocol. In patients with a CPS ≥10 at baseline, the median EFS was longer in the PEM+SoC arm compared with that in the SoC arm (59.7 months vs. 26.9 months). The HR in this subgroup was 0.66 (95% CI: 0.49, 0.88), and the difference was statistically significant. PEM+SoC also showed a statistically significant improvement in EFS in the CPS ≥1 subgroup (HR: 0.70 [95% CI: 0.55, 0.89]). Considering the lack of EFS results in the complement subgroups for CPS ≥10 (i.e. CPS <10) and CPS ≥1 (i.e. CPS <1), as well as the small group of patients with CPS < 1,

whether there is treatment effect variation associated with perioperative pembrolizumab across CPS subgroups could not be determined.

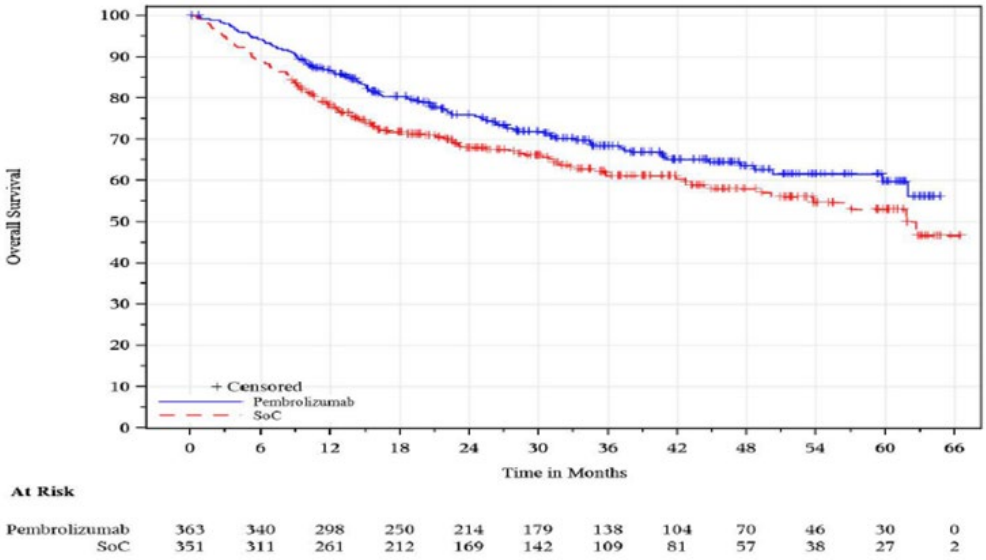
6.20 Table 5 summarises the OS results in the ITT population of KN689, with the corresponding KM plot presented in Figure 2.

Table 5: Results of OS in the KN689 trial (ITT population)

	PEM+SoC N=363	SoC N=351
Number of events (%)	113 (31.1)	131 (37.3)
Kaplan-Meier estimates (months)[a]		
Median (95% CI)	NR (61.9, NR)	61.8 (50.1, NR)
HR (95% CI)[b]	0.76 (0.59, 0.98)	
Nominal p-value[c]	0.01529	
OS rate, % (95% CI)		
At month 12	86.7 (82.7, 89.8)	77.9 (73.2, 81.9)
At month 24	75.9 (70.9, 80.1)	67.9 (62.5, 72.7)
At month 36	68.4 (62.9, 73.3)	61.1 (55.1, 66.5)
At month 48	63.6 (57.4, 69.1)	58.0 (51.6, 63.9)
At month 60	59.8 (52.4, 66.4)	52.9 (45.2, 60.0)

Source: Table 2.5-3, p74 of the submission
CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; NR = not reached; OS = overall survival; PEM = pembrolizumab; SoC = standard of care; sSAP = supplementary statistical analysis plan
Data cutoff: 25 July 2024
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by primary tumour site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumour stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.

Figure 2: Kaplan-Meier plot of OS in the KN689 trial (ITT population)



Source: Figure 2.5-3, p75 of the submission
OS = overall survival; SoC = standard of care
Data cutoff: 25 July 2024

6.21 The ESC noted that the OS data were immature at the IA1 DCO. During a median follow-up of 30.0 months for PEM+SoC and 23.4 months for SoC, death events

occurred in 113 (31.1%) patients in the PEM+SoC arm and 131 (37.3%) patients in the SoC arm. The median OS was not reached for PEM+SoC, compared with a median of 61.8 months for SoC. The OS HR estimate numerically favoured PEM+SoC (HR: 0.76 [95% CI: 0.59, 0.98]). OS in the ITT population was not formally tested per the pre-specified multiplicity strategy, as the observed p-value for OS in the CPS ≥ 10 group did not cross the multiplicity adjusted one-sided p-value boundary. The KM curves of the two treatment groups separated within the first 2 months and remained separated throughout the evaluation period when there was a reasonable number of patients remaining at risk. The PSCR stated that demonstrating a survival benefit for interventions tested in the curative setting remains inherently challenging, particularly within a reasonable timeframe. The PSCR considered the OS data sufficiently mature, noting that at the IA1 DCO 244 OS events had occurred (representing 75% of the total 324 OS events planned for the final analysis). The PSCR considered that the OS outcomes, evaluated through KM curves, landmark analyses, hazard ratios, and p-values, as well as the association demonstrated between EFS and OS, collectively suggest a consistent and clinically meaningful improvement in OS for PEM+SoC vs SoC alone. The ESC noted that the PSCR also noted similarly immature data supporting the PBAC recommendation for peri-operative early triple negative breast cancer (KN522), based on 39.1 months of follow-up, however considered that this was not a reasonable comparison due to different patient population characteristics and tumour biology.

6.22 At the IA1 DCO, mPR and pCR based on BIPR assessment were reported in 34 (9.4%) patients and 11 (3.0%) patients, respectively, in the PEM+SoC group, compared with no patients with mPR or pCR in the SoC group. The ESC noted the differences between the two treatment arms were statistically significant for both outcomes and considered this to be clinically meaningful given that these would have been determined after only 2 cycles of pembrolizumab.

6.23 The proportion of patients with high-risk features (defined as positive margins [> 1mm] or extranodal invasion) postoperatively, was measured in KN689, and the dose of adjuvant radiotherapy and use of cisplatin were determined by risk category.[14] Based on BIPR assessment, a lower proportion of patients in the PEM+SoC arm were classified postoperatively with high-risk features compared to the SoC arm (32.5% vs. 44.4%). This ESC noted that this may have enabled patients in the PEM+SoC arm to receive lower doses of radiation (60 Gy vs. 66 Gy) and a lower proportion to receive subsequent chemotherapy compared to the SoC group (29.0% vs. 39.6%). The ESC considered that these data may imply a benefit of neoadjuvant pembrolizumab.

6.24 In KN689, quality of life (QoL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of life questionnaire (QLQ)-C30

[14] Participants considered lower risk for recurrence received radiotherapy (60 Gy) plus pembrolizumab (15 cycles of 200 mg Q3W) in the pembrolizumab arm and without pembrolizumab in the SoC arm. Participants assessed have a high risk of recurrence following surgery received radiotherapy (66 Gy or 70Gy if with gross residual disease) plus concurrent cisplatin (3 cycles of 100 mg/m^2 Q3W) plus pembrolizumab (15 cycles of 200 mg Q3W) in the pembrolizumab arm and without pembrolizumab in the SoC arm.

(global health status/QoL score and physical score), the EORTC Head and Neck-Specific QoL questionnaire (EORTC QLQ-H&N35) (swallowing, speech and pain symptoms), and the EuroQoL-5 dimensions-5 levels (EQ-5D-5L) questionnaires. Results showed that health related quality of life (HRQoL) and HNSCC symptom scores remained stable during the neoadjuvant phase compared to baseline. In the post adjuvant radiotherapy ± chemotherapy phase, any score changes from baseline were generally similar between treatment groups. The submission concluded that the addition of perioperative pembrolizumab to SoC does not impact patient QoL compared to the use of SoC alone. This, however, is inconsistent with the increased adverse event (AE) profile of PEM+SoC compared with SoC alone (see the Comparative harms and Clinical claim subsections below).

Comparative harms

6.25 Table 6 presents an overall summary of AEs reported in patients who received at least one dose of study treatment, i.e. the 'all participants as treated' (APaT) population, in KN689.

Table 6: Summary of AEs in the KN689 trial (APaT population)

	PEM+SoC (N=361)	SoC (N=315)	Risk difference (95% CI)[a]	Relative risk (95% CI)[a]
Any AEs, n (%)	348 (96.4)	305 (96.8)	0.00 (-0.03, 0.02)	1.00 (0.97, 1.02)
Any Drug-related AEs, n (%)	294 (81.4)	258 (81.9)	0.00 (-0.06, 0.05)	0.99 (0.93, 1.07)
Grade ≥3, n (%)	275 (76.2)	233 (74.0)	0.02 (-0.04, 0.09)	1.03 (0.94, 1.12)
Drug related Grade ≥3, n (%)	161 (44.6)	135 (42.9)	0.02 (-0.06, 0.09)	1.04 (0.88, 1.24)
Serious AEs, n (%)	179 (49.6)	116 (36.8)	**0.13 (0.05, 0.20)**	**1.35 (1.13, 1.61)**
Drug related Serious AEs, n (%)	69 (19.1)	33 (10.5)	**0.09 (0.03, 0.14)**	**1.82 (1.24, 2.68)**
AEs Leading to drug discontinuation, n (%)	88 (24.4)	45 (14.3)	**0.10 (0.04, 0.16)**	**1.71 (1.23, 2.36)**
Drug related AEs leading to discontinuation, n (%)	64 (17.7)	39 (12.4)	0.05 (0.00, 0.11)	1.43 (0.99, 2.07)
Serious AEs leading to discontinuation, n (%)	47 (13.0)	11 (3.5)	**0.10 (0.06, 0.14)**	**3.73 (1.97, 7.06)**
Serious drug related AEs leading to discontinuation, n (%)	27 (7.5)	8 (2.5)	**0.05 (0.02, 0.08)**	**2.94 (1.36, 6.39)**
AEs leading to death, n (%)	25 (6.9)	24 (7.6)	-0.01 (-0.05, 0.03)	0.91 (0.53, 1.56)
Drug-related AEs leading to death, n (%)	4 (1.1)	1 (0.3)	0.01 (0.00, 0.02)	3.49 (0.39, 31.07)

Source: Table 2.5-12, p88 of the submission
AEs = adverse events; APaT = all participants as treated; CI = confidence interval; PEM = pembrolizumab; SoC = standard of care
Note: Statistically significant differences are **bolded**
[a] Risk differences and relative risks were calculated during the evaluation, using Stata 15

6.26 The incidence of any AEs, drug-related AEs, AEs of Grade ≥ 3, Grade ≥ 3 drug-related AEs, and AEs leading to death was similar between the treatment arms. Patients receiving PEM+SoC had a higher risk of serious adverse events (SAEs) (49.6% vs. 36.8%), AEs leading to treatment discontinuation (24.4% vs. 14.3%), and SAEs leading to discontinuation (13.0% vs. 3.5%), compared with patients receiving SoC alone. A similar trend was observed for these AE types when drug-related AEs were considered.

6.27 The most common AEs in the PEM+SoC arm were stomatitis (41.6%), radiation skin injury (39.9%), weight loss (35.7%), and anaemia (34.1%). These AEs are also the most common AEs in the comparator arm. Most of these AEs were of Grade 2 or lower. The Grade 3−5 AEs occurring in ≥10% of patients included weight decrease (13.9%), stomatitis (12.5%), dysphagia (12.2%), and anaemia (10.5%) in patients receiving PEM+SoC, and stomatitis (13.3%), neutrophil count decrease (11.7%), lymphocyte count decrease (11.4%), anaemia (11.1%), and dysphagia (10.8%) in patients receiving SoC. These common AEs were the known safety concerns of radiotherapy or cisplatin, and the incidence of these AEs did not differ greatly between the two arms.

6.28 The drug-related AEs which occurred more frequently for PEM+SoC (with ≥5% difference vs. SoC) included hypothyroidism (19.4% vs. 1.9%), rash (8.0% vs. 0.0%), pruritus (8.0% vs. 0.3%), and fatigue (18.0% vs. 13.0%). Conversely, more patients in the SoC arm reported stomatitis (52.1% vs. 38.8%), radiation skin injury (47.0% vs. 39.3%), neutrophil cell count decrease (18.7% vs. 11.6%), dysgeusia (17.8% vs. 12.7%), white blood cell decrease (15.9% vs. 10.8%), and dysphagia (15.6% vs. 10.2%) (Table 7). The most frequently reported drug-related Grade 3−5 AEs across the PEM+SoC and SoC alone arms were stomatitis (11.6% vs. 13.3%), lymphocyte count decrease (5.5% vs. 6.7%), neutrophil count decrease (5.3% vs. 11.7%), radiation skin injury (4.2% vs. 5.7%), and white blood cell decrease (3.6% vs. 8.9%). Of the reported common drug-related AEs, hypothyroidism, rash and pruritus are known AEs associated with immunotherapy. Radiation and/or chemotherapy related AEs, such as radiation skin injury, stomatitis, neutrophil count decrease, and lymphocyte count decrease, occurred at a higher rate with SoC. This could be attributable to the less intensive SoC therapy (lower radiotherapy dose and/or lower proportion of patients receiving cisplatin) observed following neoadjuvant pembrolizumab in the PEM+SoC arm.

6.29 The analysis of adverse events of special interest (AEOSIs) was the primary method of assessing immune-related adverse events (irAEs) and infusion-related reactions in KN689. The incidence of AEOSIs in the PEM+SoC and SoC groups was 43.8% and 10.8%, respectively, with drug-related AEOSI having a higher incidence in the PEM+SoC group (35.5% vs. 4.1%). The higher incidence of drug-related AEOSIs in the PEM+SoC group was driven by hypothyroidism. The most frequently reported irAEs in patients receiving PEM+SoC were hypothyroidism (24.7%), hyperthyroidism (8.9%), pneumonitis (5.5%), severe skin reactions (2.8%), colitis (2.5%) and hepatitis (2.2%), with all these AEs reported more frequently in patients receiving PEM+SoC than those treated with SoC only (Table 7). Most AEOSIs were Grade 1−2 in severity. The Grade 3−5 AEOSIs which occurred in more than five patients treated with PEM+SoC included colitis (n=8 [2.2%]), hepatitis (n=7 [1.9%]), pneumonitis (n=6 [1.7%]), and severe skin reaction (n=6 [1.7%]). One participant died due to a drug-related irAE (pneumonitis) in the PEM+SoC group.

Table 7: Drug-related AEs and AEOSIs in the KN689 trial (APaT population)

	PEM+SoC N=361	SoC N=315
Drug-related AEs (incidence ≥ 10% in either treatment arm or ≥ 5% difference in incidence between treatment arms), n (%)		
Radiation skin injury	142 (39.3)	148 (47.0)
Stomatitis	140 (38.8)	164 (52.1)
Hypothyroidism	70 (19.4)	6 (1.9)
Fatigue	65 (18.0)	41 (13.0)
Nausea	64 (17.7)	67 (21.3)
Dry mouth	63 (17.5)	68 (21.6)
Dysgeusia	46 (12.7)	56 (17.8)
Neutrophil cell count decrease	42 (11.6)	59 (18.7)
Lymphocyte count decreased	41 (11.4)	28 (8.9)
White blood cell decrease	39 (10.8)	50 (15.9)
Vomiting	39 (10.8)	25 (7.9)
Dysphagia	37 (10.2)	49 (15.6)
Weight decrease	35 (9.7)	34 (10.8)
Anaemia	32 (8.9)	34 (10.8)
Pruritus	29 (8.0)	1 (0.3)
Rash	29 (8.0)	0 (0.0)
AEOSIs (incidence ≥ 2% in either treatment arm), n (%)		
Hypothyroidism	89 (24.7)	17 (5.4)
Hyperthyroidism	32 (8.9)	10 (3.2)
Pneumonitis	20 (5.5)	0 (0.0)
Severe skin reactions	10 (2.8)	2 (0.6)
Colitis	9 (2.5)	1 (0.3)
Hepatitis	8 (2.2)	1 (0.3)

Source: Table 2.5-14, p91 and Figure 2.5-10, p97 of the submission; Table 14.3-66, pp1242-1243 of the KN689 clinical study report (dated 9 December 2024).
AEOSIs = adverse events of special interest; AEs = adverse events; APaT = all participants as treated; PEM = pembrolizumab; SoC = standard of care

6.30 The ESC noted there had been 4 (1.1%) drug-related AEs leading to death in the PEM+SoC arm compared with 1 (0.3%) in the SoC arm.

6.31 The submission did not separate the rate of AEs that occurred in the neoadjuvant and adjuvant phases of treatment. However, the United States (US) Food and Drug Administration (FDA) safety advice for pembrolizumab provides some stratification by treatment phases for HNSCC. The ESC noted that the advice shows that the majority of common (>20%) AEs in KN689 occurred during the neoadjuvant phase of treatment (US FDA, 2014[15]).

6.32 Overall, the ESC considered that the AE results reported in KN689 were consistent with the well-established safety profile of pembrolizumab, radiotherapy, and cisplatin. No new safety concerns were observed.

[15] US food and Drug Administration (FDA) (2014), Keytruda (pembrolizumab). Highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf

Benefits/harms

6.33 A summary of the comparative benefits and harms for perioperative PEM+SoC compared with SoC is presented in Table 8.

Table 8: Summary of comparative benefits and harms for PEM+SoC versus SoC[a]

Benefits (ITT population)				
	PEM+SoC	**SoC**	**Absolute difference**	**HR (95% CI)**
EFS				
EFS events, n/N (%)	136/363 (37.5)	159/351 (45.3)	–	**0.73 (0.58, 0.92)**
Median EFS, months (95% CI)	51.8 (37.5, NR)	30.4 (21.8, 50.1)	21.4	**p=0.00411**
EFS at 12 months, % (95% CI)	75.1 (70.0, 79.4)	62.5 (56.9, 67.5)	12.6	
EFS at 24 months, % (95% CI)	65.0 (59.4, 70.1)	54.6 (48.7, 60.1)	10.4	
EFS at 36 months, % (95% CI)	57.6 (51.5, 63.3)	46.4 (40.0, 52.5)	11.2	
EFS at 48 months, % (95% CI)	52.0 (45.1, 58.4)	44.2 (37.5, 50.8)	7.8	
OS				
Deaths, n/N (%)	113/363 (31.1)	131/351 (37.3)	–	0.76 (0.59, 0.98)
Median OS, months (95% CI)	NR (61.9, NR)	61.8 (50.1, NR)	NE	Nominal
				p=0.01529
Alive at 12 months, % (95% CI)	86.7 (82.7, 89.8)	77.9 (73.2, 81.9)	8.8	
Alive at 24 months, % (95% CI)	75.9 (70.9, 80.1)	67.9 (62.5, 72.7)	8.0	
Alive at 36 months, % (95% CI)	68.4 (62.9, 73.3)	61.1 (55.1, 66.5)	7.3	
Alive at 48 months, % (95% CI)	63.6 (57.4, 69.1)	58.0 (51.6, 63.9)	5.6	
Alive at 60 months, % (95% CI)	59.8 (52.4, 66.4)	52.9 (45.2, 60.0)	6.9	

Harms (APaT population)						
	PEM+SoC n/N	**SoC n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				PEM+SoC	**SoC**	
SAEs	179/361	116/315	**1.35 (1.13, 1.61)**	49.6	36.8	**0.13 (0.05, 0.20)**
AEs leading to discontinuation	88/361	45/315	**1.71 (1.23, 2.36)**	24.4	14.3	**0.10 (0.04, 0.16)**
Drug-related AEs	275/361	233/315	1.03 (0.94, 1.12)	76.2	74.0	0.02 (-0.04, 0.09)
Grade ≥ 3 drug-related AEs	161/361	135/315	1.04 (0.88, 1.24)	44.6	42.9	0.02 (-0.06, 0.09)
AEOSIs	158/361	34/315	**4.05 (2.89, 5.69)**	43.8	10.8	**0.33 (0.27, 0.39)**

Source: Table 2.5-1, p69, Table 2.5-3, p74, Table 2.5-12, p88, and Table 2.5-20, p96 of the submission.
AEs = adverse events; AEOSIs = adverse events of special interest; APaT = all participants as treated; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; NE = not estimable; NR = not reached; OS = overall survival; PEM = pembrolizumab; RD = risk difference; RR = relative risk; SAEs = serious adverse events; SoC = standard of care
Statistically significant differences are **bolded**
[a] Efficacy and safety data were from the KN689 trial at IA1, with a median follow-up of 30.0 months for PEM+SoC and 23.4 months for SoC (pooled 27.1 months)

6.34 On the basis of direct evidence presented by the submission, for every 100 patients treated with pembrolizumab, as neoadjuvant therapy followed by post-surgery adjuvant therapy in combination with SoC, in comparison with SoC, over a median follow-up of 27.2 months:

- Approximately 11 additional patients will be event-free (disease recurrence, disease progression or death) at 36 months.
- Approximately 6 additional patients will be alive at 48 months.
- Approximately 13 additional patients will experience a serious adverse event.

- Approximately 33 additional patients will experience an immune-related adverse event or infusion-related reaction.

Clinical claim

6.35 The submission described PEM+SoC as superior in terms of efficacy and inferior but manageable in terms of safety compared to SoC alone.

6.36 The ESC considered that the claim of superior efficacy of PEM+SoC compared with SoC was partially supported by the evidence presented in the submission and considered that the magnitude of clinical benefit had been overestimated for the following reasons:

- The immaturity of the OS data at the IA1 DCO of KN689. Longer-term data are required to determine whether the observed improvement in EFS translates into a statistically significant and clinically meaningful OS benefit.
- The applicability of the comparator SoC arm of the trial to Australian clinical practice. Pembrolizumab and nivolumab are currently listed on the PBS for the treatment of recurrent or metastatic HNSCC. The ESC considered that in KN689, the proportion of patients in the SoC who experienced disease progression/recurrence and subsequently received immunotherapy was much lower than that expected in the Australian setting. Consequently, OS estimates from KN689 may not reflect Australian clinical practice, and so the proposed comparative survival gain will have been overestimated.

6.37 The ESC considered that the claim of inferior safety of PEM+SoC compared with SoC alone was supported by the evidence presented in the submission.

6.38 The PBAC considered that the claim of superior comparative effectiveness was reasonable, noting that the observed difference in OS in KN689 would likely to be smaller in the Australian clinical setting.

6.39 The PBAC considered that a claim of inferior comparative safety was reasonable.

Economic analysis

6.40 The submission presented a stepped economic evaluation for the use of PEM+SoC for the treatment of LA HNSCC based on the direct, randomised KN689 trial that compared PEM+SoC to SoC alone.

6.41 The key components of the economic evaluation are summarised in Table 9.

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

Component	Summary
Treatments	Pembrolizumab + SoC versus SoC only
Time horizon	25 years in the base case vs a median follow-up for OS of 27.1 months in KN689.
Outcomes	LYs gained, QALYs gained
Methods used to generate results	Markov cohort model
Health states	Four health states: event free (EF), local recurrence (LR), incurable recurrence or progression (IRP) and dead (D).
Cycle length	1 week, with half cycle correction for outcomes and costs.
Transition probabilities and extrapolation	A multistate parametric modelling approach was used to derive the transition probabilities. This was based on patient level data from IA1 of the KN689 trial, July 2024 data cut for all health states. Time varying transition probabilities from the EFS health state were derived from extrapolations of individual patient-level data for both arms of the KN689 trial. Parametric functions were fitted to the observed KM data and chosen based on clinical plausibility, visual fit and goodness of fit using the MSE method. In the base case, transitions were modelled using the log-logistic (EF → LR), Gompertz (EF → IRP) and generalised gamma (EF →death) parametric functions. For transitions from the LR and IRP health states (LR → IRP & death; IRP → death), exponential rates of the underlying hazard functions based on patient level data were applied. All transitions to the death health state were supplemented by background mortality. Observed KM data were not directly used in the economic model and the economic model did not allow for the use of KM data. Treatment waning was applied to EFS from Year 7 to Year 10 in the base case analysis. This was done by converging the transition probabilities (from the EF health state) in the PEM+SoC arm to that of the SoC arm.
Health related quality of life	Utility values for the EF, LR and IRP health states were derived using EQ-5D-5L data from the KN689 trial and were translated using the Canadian (base case) and Australian (scenario analysis) preference sets. To avoid double counting (as disutility due to AEs was included in the base case), the utility value for the EF health state was based on HRQoL data of patients who were progression-free and not experiencing a grade 3+ AE from the KN689 trial. EF = 0.834; LR = 0.767; IRP = 0.753. Weighted disutilities of -0.01959 and -0.01868, for AEs of grade 3+, were applied in the first cycle of the model across the PEM+SoC and SoC arms, respectively. This weighting was based on the incidence of AEs observed in the KN689 trial, the mean duration of each episode, and a disutility of -0.031 (assumed for all grade 3+ AEs).
Subsequent treatment assumptions	Costs for subsequent treatment were included in both arms as a one-time cost upon entry into the IRP health state. The model included first-line and later-line treatment options based on treatment regimens that are available on the PBS. The submission assumed that 100% and 35% of patients that progressed to the IRP health state would receive 1L and 2L subsequent treatments, respectively (1L treatment following progression to recurrent/metastatic disease and 2L treatment following progression of recurrent/metastatic disease). Immunotherapies (nivolumab and pembrolizumab) were included as 1L treatments while chemotherapy regimens were included as 2L subsequent treatments in the SoC arm. Only chemotherapy regimens were included as subsequent treatments (1L and 2L) in the PEM+SoC arm in line with the “once in a lifetime rule” for the majority of immunotherapies that are PBS listed in Australia.
Costs	Direct treatment costs, costs for disease management, subsequent treatment costs, costs for treatment of AEs and terminal care costs were included.

Source: tabulated during the evaluation.

1L = first line; 2L = second line; AE = adverse event; AEs = adverse events; EF = event free; EFS = event-free survival; EQ-5D-5L = EuroQoL 5-dimension 5-level; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; IRP = incurable recurrence or progression; KM = Kaplan-Meier; LR = local recurrence; LY = life year; MSE = mean squared error; OS = overall survival; QALY = quality adjusted life year ; SoC = standard of care

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

6.42 The submission constructed a Markov model which included four health states: event-free (EF), local recurrence (LR), incurable recurrence/progression (IRP) and death. All patients entered the model in the EF health state and received either PEM+SoC or SoC. A time horizon of 25 years was nominated in the base case analysis, based on a median follow-up for OS of 27.1 months in the KN689 trial. The ESC noted that the median age of diagnosis is 65 years and that this patient population often has multiple comorbidities. For these reasons, the ESC considered a time horizon of 15 years may be more appropriate. The pre-PBAC Response provided a revised base case that included a shorter time horizon of 20 years (see paragraph 6.66 and Table 14). The pre-PBAC Response considered that a 15-year time horizon would be overly conservative given the early setting of disease and also considered that it would be inconsistent with previous economic models considered for pembrolizumab, where 25 and 30 years, had been accepted.

6.43 The submission utilised a multistate parametric modelling approach to estimate the transition probabilities in the economic model, as described by Williams, Lewsey, Briggs and Mackay (2017)[16] and Williams, Lewsey, Mackay and Briggs (2017)[17]. Independent parametric functions were fitted to the observed trial data across both treatment arms based on visual fit, clinical plausibility and goodness of fit using the mean squared error (MSE) method of the extrapolated curves. This was not complemented by goodness of fit using Akaike information criterion (AIC) values as model complexity is not taken into consideration when calculating AIC values. The economic model also allowed for the use of dependent parametric models (assuming time constant and time varying treatment effects). However, the proportional hazards assumption was not tested in the submission. Transitions to the death health state were set to equal the maximum of the transitioning probabilities and background mortality which the evaluation considered was appropriate.

6.44 KM data from the KN689 trial was not directly used in the economic model and the model did not allow for its use. This is not in line with the PBAC Guidelines (Version 5.0) which notes the preference of observed time-to-event data (up to the time point at which observed data become unreliable) over modelled data for extrapolation. The PSCR noted that model extrapolations and transition probabilities were based on survival analyses of KN689 individual patient-level data and therefore, the use of KM data for the observed model portion is expected to have minimal impact. The PSCR

[16] Williams C, Lewsey JD, Briggs AH, Mackay DF. Cost-effectiveness Analysis in R Using a Multi-state Modeling Survival Analysis Framework: A Tutorial. Medical Decision Making. 2017;37(4):340-52.

[17] Williams C, Lewsey JD, Mackay DF, Briggs AH. Estimation of Survival Probabilities for Use in Cost-effectiveness Analyses: A Comparison of a Multi-state Modeling Survival Analysis Approach with Partitioned Survival and Markov Decision-Analytic Modeling. Medical Decision Making. 2017;37(4):427-39.

also noted that OS KM data had not been applied and was modelled indirectly due to the Markov structure of the model.

6.45 In the base case, log-logistic models were selected for transitions from the EF to LR health state, Gompertz models were selected for the transitions from the EF to IRP health states and generalised gamma models were selected for transitions from the EF to death health state. These transition probabilities jointly determined the EFS endpoint and patients that did not have an EFS failure event were censored at the date of their last disease assessment. Although the submission adopted an independent parameterised approach, the same parametric functions were utilised to model both arms for each of transitions from the EF health state in both treatment arms. The ESC agreed with the evaluation that this was not well justified in the submission. Further, given that three parametric functions jointly determined the EFS composite endpoint in the base case analysis, it was difficult to evaluate the impact of the choice of parametric functions for the individual transitions from the EF health state.

6.46 The combination of log-logistic/Gompertz/generalised gamma models was the 10th best fitting combination and was used in the base case analysis. This combination of parametric functions generated higher OS rates at year 10 (37.8% and 32.1% across the PEM+SoC and SoC arms, respectively) compared to published 10-year survival rates of 22−28% for patients with locally advanced head and neck cancers (Chakrabandhu et al 2021; Santos et al 2021)[18,19]. The ESC noted and agreed with the PSCR that the studies cited by the evaluation were based in Thailand and Brazil and given differences in ethnicity, treatment access, health infrastructure and background mortality, the 10-year survival rates reported are not likely to be comparable to outcomes expected within the Australian health system.

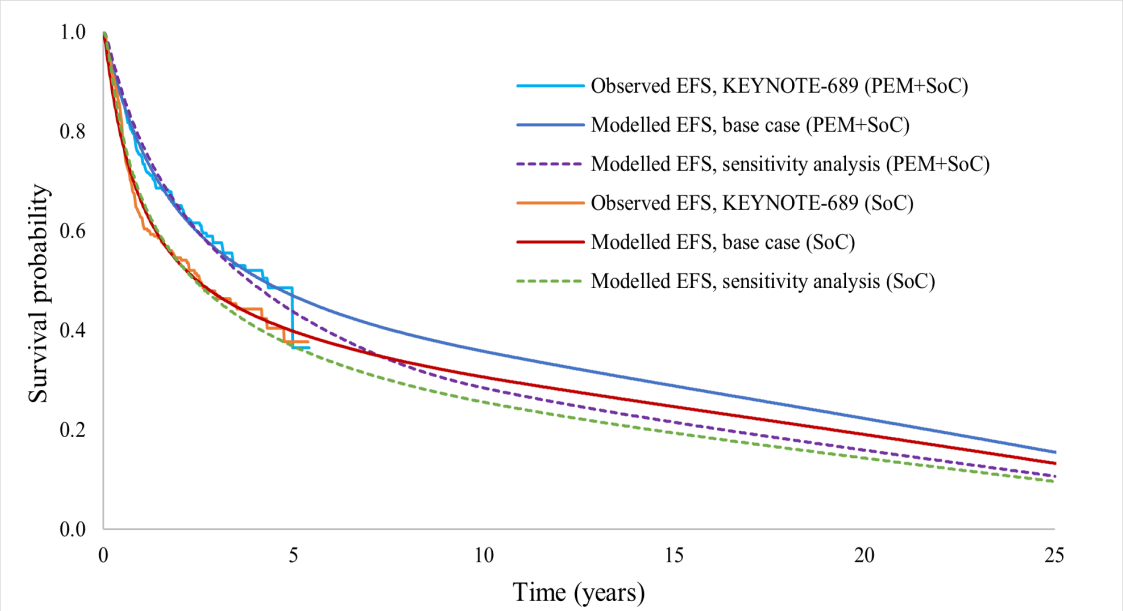
6.47 Overall survival was calculated as 1 minus the proportion transitioning to the death health state from all other health states (EF, LR and IRP). Thus, the evaluation considered that the utilisation of more conservative extrapolations to estimate the transition probabilities from the EF health may be appropriate. The evaluation noted that when an alternate combination of parametric functions is chosen (PEM+SoC: exponential/ generalised gamma/ generalised gamma; SoC: log-logistic/ generalised gamma/ generalised gamma), the resulting OS rates at year 10 are 31.9% (PEM+SoC) and 27.7% (SoC) and the modelled EFS curves appeared more clinically plausible long-term (Figure 3). This combination of parametric functions increased the base case incremental cost-effectiveness ratio (ICER) from $25,000 to < $35,000 per quality adjusted life year (QALY) gained to $35,000 to < $45,000 per QALY gained. The PSCR noted that the base case parametric extrapolation functions were selected following a systematic process that considered statistical fit, clinical plausibility and

[18] Chakrabandhu S, Bunyatisai W, Sripan P, Traisathit P, Chitapanarux I. Five- and ten-year survival of squamous cell carcinoma of the head and neck in northern Thailand: a multivariate analysis. Journal of Radiotherapy in Practice. 2021;20(4):413-8.

[19] Santos FMd, Viani GA, Pavoni JF. Evaluation of survival of patients with locally advanced head and neck cancer treated in a single center. Brazilian Journal of Otorhinolaryngology. 2021 2021/01/01/;87(1):3-10.

validation/consistency with observed and external data and were the most conservative of all the clinically plausible combinations considered. The pre-PBAC Response additionally noted that the combination of parametric functions selected by the evaluation appeared to be chosen without methodological basis and considered that it resulted in overly conservative long-term OS in the SoC arm compared with relevant literature.

Figure 3: Modelled vs KM EFS curves (both treatment arms)



Source: constructed during the evaluation, from the "Attachment 5 CEA" Workbook provided in the submission.
EFS = event-free survival; KM = Kaplan-Meier; PEM = pembrolizumab; SoC = standard of care.

6.48 Overall, the ESC noted that a substantial OS benefit had been modelled over a long time horizon (25 years), and that this benefit was based on immature OS data which may not accurately reflect outcomes that would occur in Australian clinical practice (see paragraphs 6.13 and 6.36). The ESC also noted that OS convergence was not incorporated into the model and considered this likely to be inappropriate. The pre-PBAC Response provided a revised base case which resulted in a smaller OS benefit (see paragraph 6.63). The pre-PBAC Response also stated that applying OS convergence in the locally advanced setting would not be appropriate given the relatively long survival observed for patients in this setting and the curative intent of treatment.

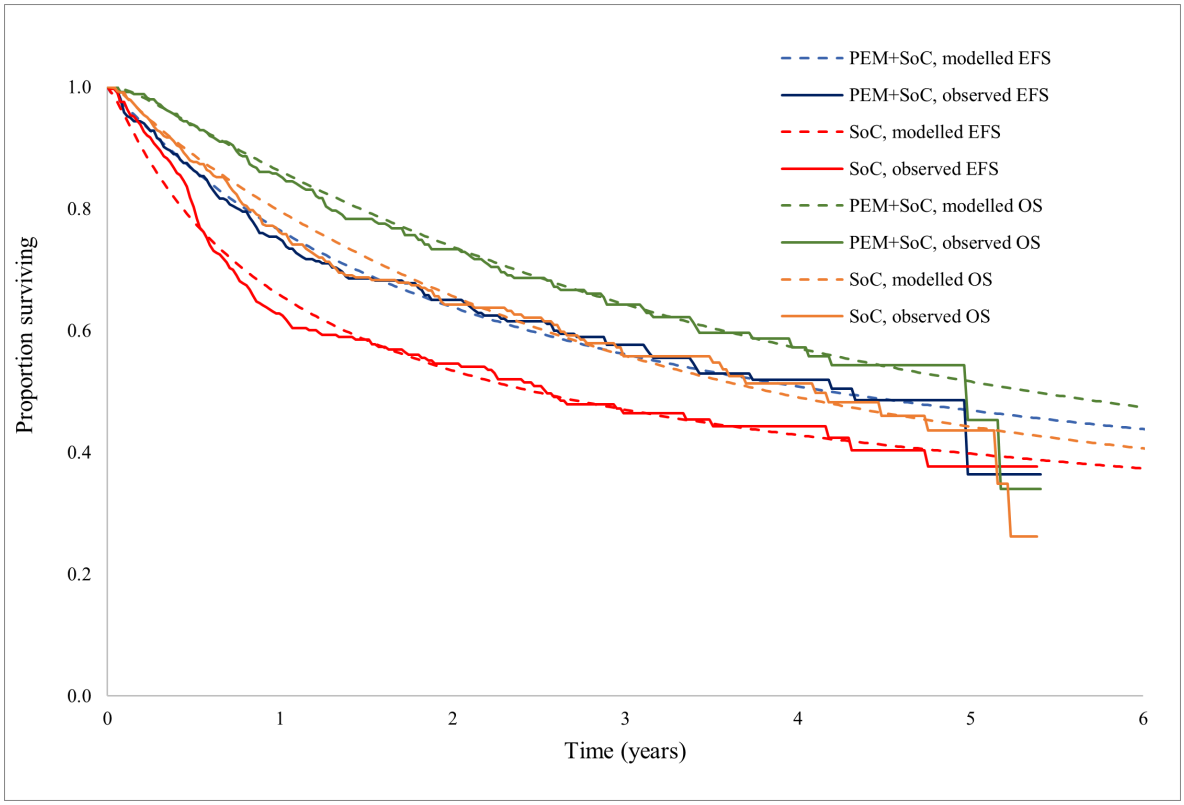
6.49 For transitions from the LR and IRP health states, exponential models were fitted to the observed data from the KN689 trial and applied to the base case analysis. The modelled curves provided a good fit to the observed data from the KN689 trial. However, these extrapolations were based on fewer patients that experienced relatively early recurrence in the trial, i.e., 104 and 116 patients in the LR and IRP health states, respectively. The PSCR noted that clinical experts were consulted during model development and indicated that most disease recurrences following surgery for LA HNSCC occur within 5 years (and therefore within the trial follow up period) and an

Australian Advisory Board confirmed that the recurrence patterns modelled were generalisable to the Australian population. The Response also noted that across both arms of KN689, the observed cumulative incidence curves for EF→LR and EF→IRP plateaued over time, indicating that hazard rates of disease relapses had subsided by the end of the available trial period and therefore the evidence collectively suggests that most disease relapses occur early. However, the ESC considered the applicability of the observed extrapolations to the broader treated population remained uncertain.

6.50 Treatment waning was applied to EFS from year 7 to year 10 in the base case analysis. This was done by converging the transition probabilities (from the EF health state) in the PEM+SoC arm to that of the SoC arm. Therefore, despite that treatment is administered for a maximum of one year, treatment effect of pembrolizumab was assumed to persist without waning for a further 6 years.

6.51 To validate the operation of the model, the submission presented a comparison of observed EFS and OS data (calculated as 1 minus the proportion transitioning to the death health state) from the KN689 trial to the modelled curves used in the base case analysis (Figure 4). However, as noted previously, the OS data from the KN689 trial were immature and the long-term overall survival rates projected by the model appeared overestimated.

Figure 4: Modelled vs KM EFS and OS curves (both treatment arms, trial time horizon)



Source: constructed during the evaluation, from the "Attachment 5- CEA" Workbook provided in the submission.
EFS = event-free survival; KM = Kaplan-Meier; OS = overall survival; PEM = pembrolizumab; SoC = standard of care

6.52 Utility weights of 0.834, 0.767 and 0.753 were applied in the EF, LR and IRP health states, respectively, which were derived from the HRQoL assessments of the KN689 trial, using the EQ-5D-5L and mapped using the Canadian value set. To avoid double counting (as disutility due to AEs was included in the base case), the utility value for the EF health state was based on HRQoL data of patients who were progression-free and not experiencing a grade 3+ AE from the KN689 trial. For the base case analysis, it may have been more reasonable to utilise utility values based on the Australian preference set. Further, the utility values applied to patients in the LR and IRP health states were based on HRQoL data for a small number of patients (n=38 for curable recurrence and n=66 for incurable recurrence, N=661). Thus, the utility values utilised in the submission are not likely to accurately reflect the quality-of-life of patients with local or incurable recurrence.

6.53 A weighted disutility of -0.01959 and -0.01868, for AEs of grade 3+, were applied in the first cycle of the model across the PEM+SoC and SoC arms. The weighting was based on the incidence of AEs observed in the KN689 trial, the duration of each episode, and an associated disutility of -0.031 (assumed for all grade 3+ AEs). The ESC agreed with the evaluation that applying a single disutility (-0.031) to all grade 3+ AEs was not reasonable, as their QoL impacts are likely to vary and the weighting calculation would be unlikely to account for these differences. Noting that the HRQoL data in the trial did not reflect the higher rate of discontinuations or serious adverse events in the PEM+SoC arm compared to SoC, the evaluation considered that it may have been more reasonable in this case to estimate disutility for the AEs from external sources.

6.54 The treatment costs were estimated based on the time-on-treatment curves for neoadjuvant therapy (pembrolizumab, 200 mg Q3W for 2 cycles) and adjuvant therapy with PEM+SoC, with or without cisplatin, Q3W for 3 cycles, followed by pembrolizumab monotherapy for up to 15 cycles (200 mg, Q3W). While the proposed restriction allows for Q3W dosing or Q6W dosing of pembrolizumab, the economic model assumed that all patients would receive the Q3W dose.

6.55 Surgery and radiation therapy costs were based on AR-DRG codes. The proportion of patients that underwent surgery and radiation therapy was derived from the KN689 trial. However, the submission applied initial surgery costs to 89.5% and 97.5% of patients across both treatment arms, calculated as a proportion of patients that were treated (361 and 315 patients in the PEM+SoC and SoC arms, respectively). However, since the modelled costs and outcomes were based on all randomised patients (363 and 351 patients in the PEM+SoC and SoC arms, respectively), costs for surgery should have been applied to the proportion of randomised patients that underwent surgery in the KN689 trial, i.e., 88.7% (n=322) and 87.75% (n=308) of patients randomised to the PEM+SoC and SoC arms, respectively. When surgery costs are applied to these proportions of patients estimated in the trial, the ICER increases by 10%. The pre-PBAC Response provided a revised base case with this change included (see paragraph 6.66; Table 14).

6.56 The evaluation considered that costs associated with subsequent treatments were likely overestimated (in both arms). Subsequent treatment costs for 1L and 2L treatment of recurrent or metastatic HNSCC were included in the base case analysis. Costs for 1L and 2L treatments were applied as a one-off cost to 100% and 35% of patients that transitioned to the IRP health state in each cycle, respectively. The ICER was sensitive to the proportion of patients treated with subsequent treatments due to the inclusion of more expensive therapies (immunotherapy) in the SoC arm. The duration and distribution of subsequent treatments was based on the KN689 trial and Australian clinical practice. Since nivolumab is listed on the PBS for the treatment of recurrent/metastatic (RM) HNSCC in patients that progress within 6 months of the last dose of platinum-based chemotherapy (PBC), the model applied costs of nivolumab treatment to all patients that progressed within 6 months in the SoC arm. Patients that progressed after 6 months of PBC could receive either pembrolizumab monotherapy (64%) or pembrolizumab in combination with cisplatin (36%). The evaluation considered that this percentage split was appropriate, however considered that it may not be reasonable to assume that all patients in the SoC arm will receive subsequent immunotherapy in the IRP health state. In the KN689 trial, only 50.5% of patients who experienced a recurrence in the SoC arm were treated with immunotherapy. It is likely that around 80−90% of patients that progress to recurrent or metastatic disease will be treated with immunotherapy due to declining performance status (paragraph 4.21, nivolumab PSD, March 2022 PBAC meeting). Furthermore, while the submission adjusted costs associated with increased use of immunotherapy, it did not adjust for the benefits associated with this increased use in the SoC arm. This was not appropriate, as the cost of SoC has been increased without including the benefit of additional treatment. Furthermore, in the KN689 trial almost 1 in 5 patients that experienced progression in the PEM+SoC arm received further immunotherapy (18.9%), outcomes for these patients were therefore included in the economic model (and the cost was not). However, the ESC considered that the clinical benefit from IO re-treatment would likely be minimal.

6.57 The pre-PBAC Response provided a revised base case which reduced the percentage of patients receiving subsequent therapy in both arms of the model to 80% and changed transition probabilities for IRP à Dead so that they were derived from the HRs for OS comparing pembrolizumab containing treatments to chemotherapy regimens for the treatment of RM HNSCC instead of KN689 trial data (see paragraph 6.66; Table 14).

6.58 Costs for routine monitoring, management of AEs, disease management and terminal care were also included in the base case. Disease management costs in the EF health state were only included for the first 5 years of the model. The basis of this assumption was not adequately justified in the submission. Furthermore, the estimated frequency of medical resource use in the EF (beyond year 1) and LR health states, i.e., once every 12 months, may not be plausible as patients will likely require increased monitoring, particularly following disease recurrence. Given that the OS data at IA1 data cut is immature, it may have been reasonable to exclude terminal care costs. Exclusion of

terminal care costs had a minimal impact on the ICER (increased by 1%). Overall, the evaluation considered the costs associated with disease management were likely underestimated in the base case analysis.

6.59 The key drivers of the economic model are summarised in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained
Transition probabilities for IRP → Dead	Using KN689 trial data to estimate the transition probabilities was reasonable. However, the use of immunotherapies in the SoC arm in the trial was lower than that expected in clinical practice. Therefore, the SoC arm likely underperformed clinical practice.	High, favours PEM+SoC. If the transition probabilities are derived from the HRs for OS comparing pembrolizumab containing treatments to chemotherapy regimens for the treatment of RM HNSCC, the ICER increases to $[redacted][2]/QALY. The pre-PBAC Response provided a revised base case with this change applied to the model.
Proportion of patients undergoing surgery	Costs for initial surgery applied to 89.5% and 97.5% of patients in the PEM+SoC and SoC arms.	Moderate, favours PEM+SoC. Changing the proportion of patients that underwent surgery in both arms to reflect the randomised population of the KN689 trial (88.7% and 87.7%) increases the ICER to $[redacted][2]/QALY. The pre-PBAC Response provided a revised base case with this change applied to the model.
Extrapolation of transition probabilities associated with the EF health state	The log-logistic/Gompertz/generalised gamma combination was utilised in the base case analysis to model transitions from the EF to the LR, IRP and death health states, respectively, across both treatment arms.	Moderate, favours PEM+SoC. Alternate combinations of parametric functions had varied impacts on the ICER.
Use of subsequent treatments	100% use on progression to the IRP health state in both treatment arms.	Moderate, favours PEM+SoC. Reducing subsequent therapy utilisation to 80% in both arms of the model increases the ICER to $[redacted][2]/QALY. The pre-PBAC Response provided a revised base case with this change applied to the model.
Time horizon	25 years in the base case, based on a follow-up for OS of 27.1 months at the time of the interim analysis 1.	Moderate, favours PEM+SoC. Decreases in the time horizon led to increases in the ICER. The pre-PBAC Response provided a revised base case with a time horizon of 20 years.

Source: tabulated during the evaluation.

2L = second line; EF = event free; HRs = hazard ratios; ICER = incremental cost-effectiveness ratio; IRP = incurable recurrence or progression; OS = overall survival; PEM = pembrolizumab; QALY = quality adjusted life year; RM = recurrent / metastatic; SoC = standard of care

The redacted values correspond to the following ranges:

[1] *$25,000 to < $35,000*

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

6.60 The results of the stepped economic evaluation are presented in Table 11.

Table 11: Results of the stepped economic evaluation

Step and component	PEM+SoC	SoC	Increment
Step 1: trial-based costs and outcomes (5.4 years)			
Costs	$[redacted]	$44,790	$[redacted][1]
LYG	3.46	3.11	0.35
Incremental cost/LY gained			$[redacted][2]
Step 2: time horizon extended to 25 years			
Costs	$[redacted]	$46,066	$[redacted][1]
LYG	6.74	5.89	0.84
Incremental cost/LY gained			$[redacted][3]
Step 3: incorporation of medical resource costs			
Costs	$[redacted]	$54,582	$[redacted][1]
LYG	6.74	5.89	0.84
Incremental cost/LY gained			$[redacted][3]
Step 4: utility weights applied			
Costs	$[redacted]	$54,582	$[redacted][1]
QALYs	5.56	4.85	0.71
Incremental cost/QALY gained (base case)			**$**[redacted][3]

Source: Table 3.8-2, p159 of the submission.
LY = life year; LYG = life-years gained; PEM = pembrolizumab; QALY = quality adjusted life year; SoC = standard of care
The redacted values correspond to the following ranges:
[1] *$15,000 to < $25,000*
[2] *$55,000 to < $75,000*
[3] *$25,000 to < $35,000*

6.61 The majority of the costs were accrued in the first 5 years of the model for both treatment arms while approximately 80.5% of the incremental life years (LYs) were gained in the extrapolated period. The disaggregated costs and outcomes for the economic analysis are presented in Table 12.

Table 12: Disaggregated summary of costs and health outcomes (discounted)

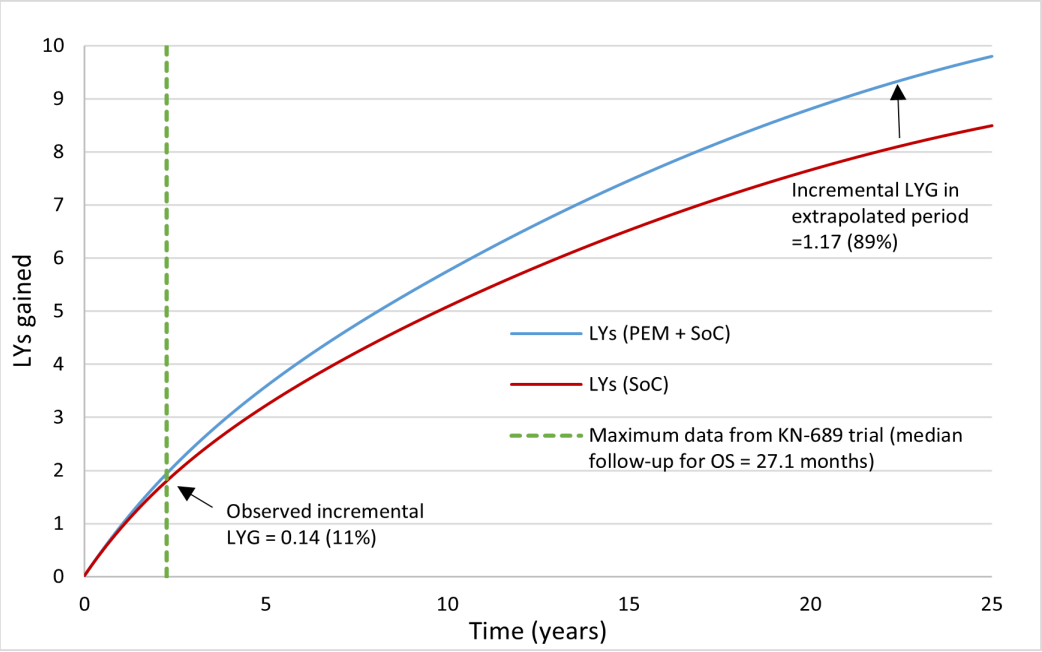
Resource item	PEM+SoC	SoC	Increment	% of increment
Costs				
Neoadjuvant/adjuvant treatment	$[redacted]	$305	$[redacted]	[redacted]%
Initial surgery and radiotherapy	$31,694	$34,960	-$3,266	-13.9%
Salvage surgery and RT in the LR state	$2,352	$2,561	-$210	-0.9%
Subsequent treatments in the IRP state	$1,360	$8,240	-$6,880	-29.3%
Management of AEs	$486	$750	-$264	-1.1%
Disease management	$3,111	$2,885	$225	1.0%
Terminal care	$4,540	$4,880	-$340	-1.4%
Total	**$**[redacted]	**$54,582**	**$**[redacted]	**100.0%**
Outcomes				
EF (LYs)	6.18	5.31	0.87	103%
LR (LYs)	0.24	0.25	-0.01	-1.4%
IRP (LYs)	0.32	0.33	-0.01	-1.7%
Total LYs	**6.74**	**5.89**	**0.84**	**100%**
EF (QALYs)	5.15	4.43	0.73	102.9%
LR (QALYs)	0.18	0.19	-0.01	-1.3%
IRP(QALYs)	0.24	0.25	-0.01	-1.5%
AE-related disutility	-0.02	-0.02	0.00	-0.1%
Total QALYs	**5.56**	**4.85**	**0.71**	**100.0%**

Source: Tables 3.8-3 and 3.8-4, pp160-161 of the submission.
AE = adverse event; AEs = adverse events; EF = event free; IRP = incurable recurrence or progression; LR = local recurrence; PEM = pembrolizumab; RT = radiation therapy; SoC = standard of care

6.62 The largest contributor to the incremental costs were the costs associated with pembrolizumab treatment in the neoadjuvant and adjuvant settings. Treatments costs were largely offset by costs of subsequent treatments in the IRP health state and costs of initial surgery and radiation therapy. Patients treated with PEM+SoC accrued substantially more benefits in the EFS health state while patients treated with SoC accrued slightly more benefits in the LR and IRP health states. This may be reasonable as patients in the SoC arm progressed more quickly and could receive immunotherapies in the IRP health state. Of note, patients would likely receive an even higher rate of immunotherapy in Australian clinical practice compared to that in the KN689 trial and therefore the incremental benefits may be lower compared to that observed in the KN689 trial (as the SoC arm in the trial is likely to be inferior to clinical practice). While the base case analysis adjusted the costs for increased use of immunotherapy, the benefits associated with this use were not adjusted for. The pre-PBAC Response provided a revised base case with the inclusion of HRs for OS comparing pembrolizumab containing treatments to chemotherapy regimens for the treatment of RM HNSCC (see paragraph 6.66; Table 14).

6.63 Figure 5 illustrates the undiscounted LYs gained over the modelled time horizon across both arms. Overall, treatment with PEM+SoC was projected to accrue an additional 1.31 LYs (undiscounted) compared to SOC alone over the modelled time horizon. The incremental LYs were reduced from 1.31 to 0.99 LYs (undiscounted) in the revised base case provided in the pre-PBAC Response.

Figure 5: LYs (undiscounted) gained over the modelled time horizon, both treatment arms



Source: constructed during the evaluation, from Sheets 'Trace_NeoAdjReg1' and 'Trace_NeoAdjReg2' of the "Attachment 5 CEA' workbook provided in the submission.
LYG = life-years gained; LYs = life-years; OS = overall survival; PEM = pembrolizumab; SoC = standard of care

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

6.65 The ESC agreed with the economic issues identified during the evaluation and noted that individual changes to inputs related to these issues did not have a significant impact on the ICER. However, overall, the ESC considered that there was substantial uncertainty associated with the economic model and that multivariate sensitivity analysis demonstrated a large cumulative effect. The ESC also noted that a 15-year time horizon and OS convergence would be appropriate to consider for inclusion, and that this would further increase the ICER. The ESC also considered that alternative extrapolation functions would be informative to show as a sensitivity analysis but noted that there may not be sufficient data to inform these.

Table 13: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change from base case
Base case	**$** [redacted]	**0.71**	**$** [redacted] 1	-
Discount rate (base case 5% costs and outcomes)				
0% costs and outcomes	$ [redacted]	1.09	$ [redacted] 2	- [redacted] %
3.5% costs and outcomes	$ [redacted]	0.79	$ [redacted] 1	- [redacted] %
Time horizon (base case 25 years)				
15 years	$ [redacted]	0.58	$ [redacted] 3	[redacted] %
20 years	$ [redacted]	0.66	$ [redacted] 3	[redacted] %
Extrapolation (base case: log-logistic/Gompertz/gen-gamma)				
PEM+SoC: exponential/gen gamma/gen gamma SoC: log-logistic/gen gamma/gen-gamma) **(#4)**	$ [redacted]	0.61	$ [redacted] 3	[redacted] %
PEM+SoC: exponential/gen gamma/Gompertz SoC: gen gamma/gen gamma/gen gamma	$ [redacted]	0.50	$ [redacted] 3	[redacted] %
PEM+SoC: exponential/Gompertz/gen gamma SoC: gen gamma/Gompertz/gen gamma	$ [redacted]	0.40	$ [redacted] 4	[redacted] %
Log-normal/Gen gamma/Gen gamma	$ [redacted]	0.83	$ [redacted] 1	- [redacted] %
Log-normal/Gompertz/Gen gamma	$ [redacted]	0.62	$ [redacted] 3	[redacted] %
Treatment effect waning (base case: between years 7 and 10)				
Waning between years 5 and 7	$ [redacted]	0.73	$ [redacted] 1	- [redacted] %
No treatment waning	$ [redacted]	0.74	$ [redacted] 1	- [redacted] %
Transition probabilities for the IRP health state (base case: using trial data)				
Using HRs for OS from external sources for immunotherapies in the SoC arm **(#5)**	$ [redacted]	0.58	$ [redacted] 3	[redacted] %
Subsequent treatment costs				
Applying costs to 80% of patients in the IRP health state **(#2)**	$ [redacted]	0.71	$ [redacted] 3	[redacted] %
Applying costs to 90% of patients in the IRP health state **(#3)**	$ [redacted]	0.71	$ [redacted] 1	[redacted] %
Applying initial surgery costs to 88.7% and 87.75% of patients across both arms **(#1)**	$ [redacted]	0.71	$ [redacted] 3	[redacted] %
Terminal care costs				
Sourced from Goldsbury, 2018	$ [redacted]	0.71	$ [redacted] 1	- [redacted] %
Excluded	$ [redacted]	0.71	$ [redacted] 1	[redacted] %
Censoring rule (base case: censored at last disease assessment)				
Censored at last date patient was known to be alive	$ [redacted]	0.70	$ [redacted] 1	[redacted] %
Utility values (base case: EF=0.835, LR=0.767, IRP=0.753)				
IRP, post-progression = 0.713 (KN048 trial) – Australian based utilities	$ [redacted]	0.76	$ [redacted] 1	- [redacted] %
EF, 0.891, LR, 0.819, IRP (pre- and post-progression), 0.806] – Australian based utilities	$ [redacted]	0.75	$ [redacted] 1	- [redacted] %
Multivariate analyses				
#1, #2	$ [redacted]	0.71	$ [redacted] 3	[redacted] %
#1, #2, #4	$ [redacted]	0.61	$ [redacted] 3	[redacted] %
#1, #2, #4, #5	$ [redacted]	0.49	$ [redacted] 5	[redacted] %

Source: tabulated during the evaluation, from Table 3.9-1, pp163-165 of the submission and the "Attachment 5 CEA" workbook provided in the submission.

AEs = adverse events; EF = event free; Gen gamma = generalised gamma; HRs = hazard ratios; ICER = incremental cost-effectiveness ratio; IRP = incurable recurrence or progression; LR = local recurrence; OS = overall survival; PEM = pembrolizumab; QALY = quality adjusted life year; SoC = standard of care

The redacted values correspond to the following ranges:

[1] *$25,000 to < $35,000*
[2] *$15,000 to < $25,000*
[3] *$35,000 to < $45,000*
[4] *$55,000 to < $75,000*
[5] *$45,000 to < $55,000*

6.66 In order to address issues raised by the ESC, the pre-PBAC Response provided a revised base case (Table 14). Revisions to the model included:

1. The percentage of patients that are applied initial surgery costs was changed from being based on the proportion of patients treated to the proportion of patients randomised, i.e., 88.7% (n=322) and 87.75% (n=308) of patients randomised to the PEM+SoC and SoC arms, respectively;
2. The percentage of patients assumed to receive subsequent treatment costs in the IRP health state (both arms) was reduced from 100% to 80% of patients;
3. The time horizon was reduced from 25 years to 20 years;
4. The source of transition probabilities for the IRP health state was changed from KN689 trial data to OS HRs (external sources) that account for the use of immunotherapies in the SoC arm; and
5. The proposed effective ex-manufacturer price of pembrolizumab was reduced from $[redacted] to $[redacted] per 100 mg vial.

Table 14: Pre-PBAC Response: revised base case

Model changes	Incremental cost	Incremental QALY	ICER	% change from base case
Base case	**$[redacted]**	**0.71**	**$[redacted][1]**	-
Applying initial surgery costs to 88.7% and 87.75% of patients across both arms **(#1)**	$[redacted]	0.71	$[redacted][2]	[redacted]%
Applying subsequent treatment costs to 80% of patients in the IRP health state (both arms) **(#2)**	$[redacted]	0.71	$[redacted][2]	[redacted]%
20 years **(#3)**	$[redacted]	0.66	$[redacted][2]	[redacted]%
Transition probabilities for the IRP health state use OS HRs accounting for immunotherapies in the SoC arm **(#4)**	$[redacted]	0.58	$[redacted][2]	[redacted]%
#1 + #2 + #3 + #4	$[redacted]	0.56	$[redacted][3]	[redacted]%
#1 + #2 + #3 + #4 + price reduction ($[redacted] net AEMP)	**$[redacted]**	**0.56**	**$[redacted][2]**	**[redacted]%**

The redacted values correspond to the following ranges:

[1] *$25,000 to < $35,000*
[2] *$35,000 to < $45,000*
[3] *45,000 to < $55,000*

Drug cost/patient/course

6.67 The total drug cost per patient per course for pembrolizumab, as estimated in the economic analysis and financial estimates, is presented in Table 15. The economic analysis and financial estimates assumed that all patients would receive the Q3W dose

in the adjuvant therapy phase. The PBAC noted the cost per patient per course using the effective price proposed in the pre-PBAC response was $[redacted].

Table 15: Drug cost per patient for pembrolizumab

	Pembrolizumab		
	Trial dose and duration	**Model**	**Financial estimates**
Mean dose	200 mg/dose	200 mg/dose	200 mg/dose
Mean duration	Neoadjuvant: 5.84 weeks (100% of patients) Adjuvant: 34.26 weeks (70.6% of patients)	Neoadjuvant: 5.84 weeks (100% of patients) Adjuvant: 34.26 weeks (70.6% of patients)	Neoadjuvant: 5.84 weeks (100% of patients) Adjuvant: 34.26 weeks (70% of patients)
Cost/patient/month	$[redacted] [a]	$[redacted] [a]	$[redacted] [b]
Cost/patient/course	$[redacted] [c]	$[redacted] [c]	$[redacted] [d]

Source: tabulated during the evaluation, from the "Attachment 5 CEA" and "Attachment 8 UCM' Workbooks provided in the submission.
[a] Based on a 4.35 week month and cost per administration of $[redacted].
[b] Assuming a 4-week month and cost per administration of $[redacted].
[c] Based on 100% of patients receiving 1.95 cycles of neoadjuvant therapy, 70.6% of patients receiving 11.42 cycles of adjuvant therapy and a cost per administration of $[redacted]. When assuming 100% of patients receive all cycles of neoadjuvant (1.95) and adjuvant therapy (11.42) the cost/patient/month increases to $[redacted] (and $[redacted] when using the effective price proposed in the pre-PBAC response).
[d] Based on 100% of patients receiving 1.95 cycles of neoadjuvant therapy, 70% of patients receiving 11.42 cycles of adjuvant therapy and a cost per administration of $[redacted].

Estimated PBS usage & financial impacts

6.68 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the number of incident patients each year who would be eligible for the proposed pembrolizumab treatment. A summary of the data sources and parameter values used to estimate the utilisation and financial impacts associated with the proposed listing of pembrolizumab for the neoadjuvant and adjuvant treatment of HNSCC is presented in Table 16.

Table 16: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident Population: People (2025–2030)	5,450 in Year 1 increasing to 5,928 in Year 6, AIHW 2024 Book1e	The population is patients with head and neck cancer (including lip).
Percentage with nasopharynx, sinus or salivary gland cancers	15%, AIHW 2024 Book 1a	The percentage was taken as the sum of nasopharyngeal, sinus, sublingual, submandibular and parotid cancers over all head and neck cancers.
Percentage with squamous cell histology (HNSCC)	93%, Foley et al, 2023	The percentage was taken from a Queensland statewide registry of head and neck cancers between 2013 and 2015.
Percentage with locally advanced disease	58%, average of 7 Australian studies and externally validated with HNSCC Advisory Board	The ESC noted that the studies included in the calculation were not always representative of the proposed PBS population (as noted in the submission). As noted in the submission, the Foley study used a different staging methodology which produces a significantly higher value. If the average, without the Foley study, is taken the percentage is 55.6%. The PSCR maintained that the inclusion of the Foley study was appropriate and noted excluding it from the calculation had minimal impact on the financial estimates.

Parameter	Value applied and source	Comment
Percentage with resectable disease who receive surgery	41%, average of 6 studies and externally validated with HNSCC Advisory Board	The percentage was derived from the case mix of the six studies, weighted by the likely resectability of the four tumour sites (as validated by an HNSCC Advisory Board). The ESC noted that this resulted in a value that is at the top of the range of values reported in the original studies. If the average of the studies is used, the value is 36%. The PSCR noted that the resectability of LA HNSCC can vary depending on tumour location, extent of invasion, and patient-specific factors such as fitness and comorbidities. Therefore, estimating the proportion of LA HNSCC largely depends on the case mix within the cohort used to inform the estimate. The Response argued that the submission reasonably used six large cohort studies to account for variation in case mix. The PSCR also noted that there was likely to be overlap between ECOG PS (85% applied in the UCM) and the criteria used to assess surgical eligibility, and including ECOG PS as a separate criterion in the financial estimates could lead to double counting, ultimately underestimating the net cost to government.
ECOG PS 0-1	85%, Tarallo et al. 2020	This percentage was taken from a study of French, Germany, UK, Spanish, Italian and US patients and validated by an HNSCC Advisory Board.
Uptake – initial treatment (neoadjuvant)	90%, assumption	The evaluation considered that given the limited alternative treatments, this level of uptake is likely to be achieved; however, it is a source of uncertainty.
Uptake – continuing treatment (adjuvant)	70% KN689 CSR IA1 Patient Disposition	The percentage was used to account for the 30% of patients who receive neoadjuvant treatment and do not later receive adjuvant treatment. This aligns with the percentages applied in the economic model.
Grandfathered patients	[redacted][1], sponsor assumption	The submission proposed the inclusion of [redacted][1] patients from a patient familiarisation program. These patients were subtracted from the incident patient population.
Total scripts	13.37 per patient over 40.10 weeks, assuming 100% compliance	This was consistent with the pivotal trial and the treatment duration applied to the economic model. For grandfathered patients, 6.68 scripts were assumed.
MBS items	$126.00 (MBS item 13950) $100.80 at 80% 1 service per script	The submission proposed inclusion of MBS Item 13950 for the administration of pembrolizumab.

Source: The financial estimates from the submission: 10. Registry population, 2a. Patients - incident, 2d. Patients - DTG, 3a. Scripts - proposed, 2c. Patients - GF, 3b. Impact - proposed (pub), 3c. Impact - proposed (eff), 2e. Scripts - market, 7. Net changes – MBS.
AIHW = Australian Institute of Health and Welfare; CEA = cost-effectiveness analysis; CSR = clinical study report; ECOG = Eastern Cooperative Oncology Group; HNSCC = head and neck squamous cell carcinoma; MBS = Medicare benefits schedule; PBS = Pharmaceutical Benefits Scheme; PS = performance status; UK = United Kingdom; US = United States
The redacted values correspond to the following ranges:
[1] < 500

6.69 The estimated use and financial impacts of listing pembrolizumab are presented in Table 17.

Table 17: Estimated impact of listing pembrolizumab

Extent of use	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Incident Population						
Head and neck cancer AIHW 2024	4,258	4,386	4,462	4,534	4,611	4,686
Locally Advanced Resectable disease and surgery ECOG PS 0-1	58% 41% 85%	58% 41% 85%	58% 41% 85%	58% 41% 85%	58% 41% 85%	58% 41% 85%
Eligible patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Uptake - initial treatment	[redacted]%	[redacted]%	[redacted]%	[redacted]	[redacted]%	[redacted]%
Neoadjuvant patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Neoadjuvant scripts [a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Uptake - adjuvant treatment based on neoadjuvant patients	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Adjuvant patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Adjuvant scripts [b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Grandfathered Population						
Patient familiarisation program	[redacted][4]					
Neoadjuvant scripts [c]	[redacted][4]					
Adjuvant scripts [d]	[redacted][4]					
Total scripts	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]

Source: The financial estimates from the submission: 10. Registry population, 2a. Patients - incident, 2d. Patients - DTG, 3a. Scripts - proposed, 2c. Patients – GF.

[a] Assuming 1.95 scripts per patient for neoadjuvant treatment

[b] Assuming 11.42 scripts per patient for adjuvant treatment

[c] Assuming 1.95 scripts per patient for neoadjuvant treatment

[d] Assuming 4.73 scripts per patient for adjuvant treatment

AIHW = Australian Institute of Health and Welfare; ECOG = Eastern Cooperative Oncology Group; HNSCC = head and neck squamous cell carcinoma; LA = locally advanced; PS = performance status

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *5,000 5o < 10,000*

[3] *5,000 to < 10,000*

[4] < 500

Table 18: Estimated financial impact of listing pembrolizumab

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net financial impact of pembrolizumab (effective price)						
Net cost to PBS/RPBS	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Net cost to MBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net cost to PBS/RPBS/MBS	**$[redacted][1]**	**$[redacted][1]**	**$[redacted][1]**	**$[redacted][1]**	**$[redacted][1]**	**$[redacted][1]**
Pre-PBAC Response (effective price) [a]						
Cost to the PBS/RPBS less copayments	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Cost offsets	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]
Net cost to MBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net cost to PBS/RPBS/MBS impact	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**

Source: The financial estimates from the submission: 3a. Scripts - proposed, 3b. Impact - proposed (pub), 3c. Impact - proposed (eff), 4b. Impact - affected (pub), 4c. Impact - affected (eff), 5. Impact - net, 7. Net changes – MBS; The financial estimates provided with pre-PBAC Response: Attachment 8 UCM - MSD Pre-PBAC (Update including cost offsets).xlsx.

MBS = Medicare benefits schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] It was noted by the Secretariat that the duration for cisplatin, carboplatin and 5-fluorouracil (5-FU) had been double counted.

The redacted values correspond to the following ranges:

[1] *$20 million to < $30 million*

[2] *$0 to < $10 million*

[3] *$10 million to < $20 million*

6.70 Based on the submission, the total PBS/RPBS impact of listing pembrolizumab was estimated to be $20 million to < $30 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing. Based on the revised financial estimates provided in the pre-PBAC Response, the total PBS/RPBS impact of listing pembrolizumab was estimated to be $10 million to < $20 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing.

6.71 The ESC noted that the submission asserted that reduction in later line treatment will occur beyond the time horizon of the financial estimates. The submission therefore did not apply any offset medicines to the financial estimates. However, based on the data reported for the pivotal trial, the median EFS is less than the 6 years used in the financial estimates. In the submission's economic model (base case), the majority of transitions to the IRP health state occurred during the first 5 years (percentage of SoC cohort, Y1: 15.6%, Y2: 4.99%, Y3: 1.94%, Y4: 0.86%, Y5: 0.44%). Not accounting for these patients is also inconsistent with the argument made to support the use observed data from the KN689 trial for transitions from the LR and IRP health states (paragraph 6.49). This indicates that it is more likely that there will be patients who progress to recurrent/metastatic disease during the modelled period. These patients

would not be eligible for pembrolizumab treatment in the metastatic setting and this offset should be captured in the financial estimates. The pre-PBAC Response provided revised financial estimates which included cost-offsets for the reduced use of immunotherapy in the recurrent/metastatic setting and a reduced price for the proposed listing of pembrolizumab (ex-manufacturer price = $[redacted] per 100 mg vial) (Table 18, Table 19).

Table 19: Number of patients ineligible for nivolumab and pembrolizumab in the metastatic setting [a]

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Pembrolizumab (34 weeks treatment duration)	[redacted] [1]	[redacted] [1]	[redacted] [1]	[redacted] [1]	[redacted] [1]	[redacted] [1]
Nivolumab (24 weeks treatment duration)	[redacted] [1]	[redacted] [1]	[redacted] [1]	[redacted] [1]	[redacted] [1]	[redacted] [1]

Source: The financial estimates provided with pre-PBAC Response: Attachment 8 UCM - MSD Pre-PBAC (Update including cost offsets).xlsx

[a] Assumes 10.2% nivolumab in the first 6 months; 5.4% pembrolizumab from 6 months to Y1, and pembrolizumab Y2: 5.0%, Y3: 1.9%, Y4: 0.8%; Y5: 0.4%; Y6: 0.3%, assuming 80% uptake.

The redacted values correspond to the following ranges:

[1] < 500

6.72 The ESC noted that the submission has only modelled Q3W treatment of patients but is seeking a Q6W listing as well. This is consistent with other pembrolizumab listings. While it should not have a material impact on the PBS/RPBS financials, it halves the MBS impact (less infusions) for every patient who is treated Q6W and should be captured in the financial estimates. The PSCR noted that it was uncertain what proportion of patients would utilise the Q3W regimen compared to Q6W and considered that including Q6W dosing in the financial estimates would have a minimal impact on the net cost to the government.

6.73 The submission included grandfathered patients who were likely to participate in the sponsor's patient familiarisation program when it is launched. These patients are drawn from the incident patient population, which is reduced by a corresponding number to avoid double counting.

6.74 The ESC noted the issues raised by the evaluation for the financial estimates and advised that updates to cost-offsets associated with immunotherapy in the recurrent/metastatic setting, Q6W dosing assumptions, and the proportion of patients with locally advanced and resectable disease should be considered. As stated previously, the pre-PBAC response provided revised financial estimates including cost-offsets for reduced immunotherapy use in the recurrent/metastatic setting.

Quality Use of Medicines

6.75 The submission recognised that the use of pembrolizumab in earlier lines of therapy require resources to ensure appropriate use in clinical practice.

6.76 The sponsor proposed to develop materials to provide the latest information to clinical professionals and patients to support the identification and management of treatment-related adverse events, in particular immune-related adverse events. In addition, the sponsor has proposed to undertake a range of education activities. These

planned programs included face to face workshop sessions at major oncology clinician and nurse conferences.

6.77 The sponsor proposed to use their existing 1800 medical information service to respond to questions from patients, carers and health care professionals regarding pembrolizumab in LA HNSCC.

Financial Management – Risk Sharing Arrangements

6.78 The submission requested amendment of the existing HNSCC risk sharing arrangement (RSA) to account for the addition of treatment in an earlier line of therapy and the subsequent reduction in the number of patients that will require treatment in the recurrent/metastatic setting. The evaluation considered that this was an appropriate method of managing residual risk across the indication. However, for this adjustment to be accurate, the financial estimates will need to accurately reflect the likely use of pembrolizumab/ nivolumab in the resectable and locally advanced setting and incorporate any relevant cost-offsets associated with immunotherapy in the recurrent/metastatic setting. The pre-PBAC response provided this information.

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

7 PBAC Outcome

7.1 The PBAC recommended pembrolizumab for the treatment of resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC). The PBAC considered that pembrolizumab commenced as neoadjuvant treatment (prior to surgical resection), followed by adjuvant treatment (after surgical resection) in combination with radiotherapy, with or without chemotherapy, and subsequently as monotherapy (PEM+SoC), improved event free survival (EFS) compared to standard of care (SoC) alone. The PBAC noted that the overall survival (OS) data were immature and the OS estimates from the key clinical trial (KEYNOTE-689) may not reflect Australian clinical practice, as the proportion of patients in the SoC arm who experienced disease progression/recurrence and subsequently received immunotherapy was lower than expected in the Australian setting and therefore the proposed comparative survival gain will have been overestimated. The PBAC accepted that the respecified base case of the economic model provided in the pre-PBAC Response had provided greater certainty and that pembrolizumab was likely cost-effective at the reduced price proposed in the Response. The PBAC considered that the financial estimates provided with the pre-PBAC Response were appropriate but required further revision to incorporate offsets to account for patients who do not progress as a result of treatment with pembrolizumab in the LA setting

7.2 The PBAC noted the consumer comments from individuals, health care professionals and Head and Neck Cancer Australia, Rare Cancers Australia, and the Medical Oncology Group of Australia (MOGA) were supportive of the proposed listing. The PBAC noted the input described the significant morbidity experienced by patients both

before and after surgery, which includes severe disfigurement, loss of vision, and impairments in the ability to swallow, speak, eat, or drink, which profoundly affect both the physical and mental wellbeing of patients. The PBAC agreed that there is high clinical need for patients living with HNSCC, noting the poor clinical outcomes and severe complications associated with current SoC. The PBAC noted comments describing the clinical meaningfulness of perioperative treatment with pembrolizumab providing the potential for a reduced risk of recurrence and morbidity associated with current SoC by minimising surgical invasiveness and reducing the intensity of adjuvant chemoradiotherapy.

7.3 In relation to the proposed listing and restriction, the PBAC advised the following:

- The inclusion of Stage IVB patients in the proposed restriction is likely reasonable, noting that a small proportion of these patients will have resectable disease (paragraph 3.7).
- In line with previous PBAC decisions, not restricting treatment to patients expressing PD-L1 remains appropriate (paragraph 3.9).
- The exclusion of tumours in the nasopharyngeal, sinus, or other para-nasal regions from the proposed PBS population was appropriate and consistent with the exclusion criteria of KN689 and with the current pembrolizumab listing for recurrent or metastatic HNSCC (paragraph 3.6).
- Revision to the wording of clinical criteria is required to allow grandfathered patients who have received non-PBS subsidised pembrolizumab to access PBS treatment (paragraph 3.4).
- Flow on changes may be required to the current pembrolizumab listing and nivolumab listing for recurrent/metastatic HNSCC to preclude retreatment with a programmed cell death 1 (PD-1) inhibitor, in line with the "once per lifetime" rule (paragraph 3.10).

7.4 The PBAC considered that the proposed comparator of SoC, consisting of adjuvant radiotherapy with or without chemotherapy, was an appropriate main comparator and noted it was also aligned with current local and international treatment guidelines.[20,21]

7.5 The PBAC noted the submission was based on one head-to-head clinical trial (KN689) which compared PEM+SoC with SoC in patients with resectable Stage III–IVA squamous cell carcinoma (SCC) of the oral cavity, pharynx or larynx (N = 714). The PBAC noted the OS data at the interim analysis 1 (IA1) data cut off (DCO) was immature and may not be applicable to Australian clinical practice (paragraphs 6.13 and 6.36). The PBAC agreed with the ESC that given the lower proportion of patients receiving immunotherapy post-recurrence in the SoC arm compared to typical Australian clinical practice, the observed difference in OS would likely be smaller in a real-world setting.

[20] eviQ. Head and neck. Cancer Institute NSW. 2025; Available from: https://www.eviq.org.au/medical-oncology/head-and-neck.

[21] National Comprehensive Cancer Network (NCCN). NCCN Guidelines Version 4.2025: Head and Neck Cancers. 2025.

7.6 The PBAC noted that PEM+SoC was associated with a statistically significant improvement in EFS compared with SoC (hazard ratio [HR]: 0.73; 95% confidence interval [CI]: 0.58, 0.92; p-value: 0.00411). The PBAC also noted in the PEM+SoC arm, major pathological response (mPR) and pathological complete response (pCR) were reported in 34 (9.4%) patients and 11 (3.0%) patients, respectively, whereas the SoC arm had no reported instances of either response. The PBAC noted other clinically important benefits reported for PEM+SoC versus SoC, including a lower proportion of patients in the PEM+SoC arm classified postoperatively with high-risk features compared to the SoC arm (32.5% vs. 44.4%), which the PBAC considered may have enabled patients in the PEM+SoC arm to receive lower doses of radiation (60 Gy vs. 66 Gy) and a lower proportion to receive subsequent chemotherapy compared to the SoC group (29.0% vs. 39.6%).

7.7 The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data, noting that the observed difference in OS in KN689 would likely be smaller in the Australian clinical setting.

7.8 The PBAC noted patients receiving PEM+SoC had a higher risk of serious adverse events (SAEs) (49.6% vs. 36.8%), AEs leading to treatment discontinuation (24.4% vs. 14.3%), and SAEs leading to discontinuation (13.0% vs. 3.5%), compared with patients receiving SoC alone. The PBAC noted that the AE results reported in KN689 were consistent with the known safety profile of pembrolizumab, radiotherapy, and cisplatin and no new safety concerns were observed. The PBAC considered a claim of inferior comparative safety was reasonable.

7.9 The PBAC noted that the submission presented a cost-utility analysis to support the cost-effectiveness of PEM+SoC versus SoC in the locally advanced setting. The PBAC acknowledged the key concerns raised by the evaluation and the ESC relating to the economic model. The PBAC noted that the OS projections in the economic model were based on immature OS data and the reported difference between the arms would likely be smaller in Australian clinical practice. Despite this, a substantial OS benefit had been modelled over a long time horizon (25 years). The PBAC also noted that the cost of subsequent immunotherapy use in the SoC arm had been overestimated and the benefit underestimated (as discussed in paragraph 6.56). The PBAC noted that these issues were key drivers in the economic model and that they had a cumulative effect on the incremental cost-effectiveness ratio (ICER).

7.10 The PBAC noted that the pre-PBAC Response provided a revised base case incorporating changes to a number of uncertain inputs in the model, including initial surgery and subsequent treatment costs, the time horizon, and transition probabilities for the IRP health state, as outlined in paragraph 6.66. The PBAC noted the justifications provided in the pre-PBAC Response for not addressing issues relating to the extrapolation of transition probabilities associated with the EF health state and the time horizon. The PBAC noted that the revised base case provided more reasonable estimates for the projected life years gained from pembrolizumab treatment versus SoC (1.31 vs. 0.99 LYs undiscounted) and considered that overall, the

revised economic model base case provided acceptable reliability. The PBAC advised that pembrolizumab was considered cost-effective at the price proposed in the pre-PBAC Response.

7.11 The PBAC noted that the submission used an epidemiological approach to estimate the utilisation and financial implications of listing pembrolizumab for the treatment of LA HNSCC. The PBAC noted that the submission's estimates assumed that all patients would be treated with pembrolizumab Q3W. While consistent with the submission's economic model, the PBAC considered that a substantial proportion of patients would prefer Q6W dosing, given the added convenience of less frequent administration. The PBAC also noted the uncertainties raised by the evaluation and the ESC related to the percentage of patients with locally advanced and resectable disease who receive surgery (Table 16). The PBAC noted the values for these parameters were not amended in the revised financial estimates provided in the pre-PBAC Response, however considered the percentages proposed initially by the submission were likely reasonable.

7.12 The PBAC noted the pre-PBAC Response provided revised financial estimates that included cost offsets for the reduction in use of immunotherapy in the recurrent/metastatic setting (due to patients being ineligible for immunotherapy retreatment after receiving pembrolizumab in the perioperative setting) and a reduced price for the proposed listing of pembrolizumab. The PBAC considered these changes were appropriate, however noted that further adjustment to offset calculations would be required. The PBAC considered that the offset calculation should be revised to account for patients who do not progress as a result of treatment with pembrolizumab in the LA setting. The PBAC also advised any revisions to utilisation should be appropriately incorporated into the broad listing proposal that will be considered at the December 2025 PBAC meeting.

7.13 The PBAC considered it would be appropriate for pembrolizumab to be included in the existing HNSCC risk sharing arrangement (RSA) in place for pembrolizumab and nivolumab in recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx with expenditure caps adjusted to account for the net cost of listing pembrolizumab for LA HNSCC (accounting for the revisions outlined in paragraph 7.12).

7.14 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for pembrolizumab:

a. The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over SoC, as while clinically relevant improvements in EFS were evident, they were moderate rather than substantial, and the overall survival benefit remains unclear;

b. The treatment is not expected to address a high and urgent unmet clinical need as there are currently PD-(L)1 inhibitors listed on the PBS for HNSCC;

c. It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.15 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 new listing as follows:

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)			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒Medical Practitioners			
Restriction type: ☒Authority Required (STREAMLINED) [new]			
Administrative Advice: No increase in the maximum amount or number of units may be authorised.			
Administrative Advice: No increase in the maximum number of repeats may be authorised			
Administrative Advice: Special Pricing Arrangements apply			
Restriction Summary [new1] / Treatment of Concept: [new1A]			
Episodicity: [blank]			
Severity: Resectable locally advanced			
Condition: Squamous cell carcinoma of the oral cavity, pharynx or larynx			
Indication: Resectable locally advanced squamous cell carcinoma of the oral cavity, pharynx or larynx			
Treatment Phase: [Blank]			
Clinical criteria:			
Patient must have stage III-IVB squamous cell carcinoma of the oral cavity, pharynx or larynx			
AND			
Clinical criteria			
Patient must have tumour(s) that are resectable as assessed by the treating clinician; OR			
Patient must have undergone surgical resection			
AND			
Clinical criteria			
Patient must have a WHO performance status of 1 or less			
AND			
Clinical criteria			
Patient must not have experienced disease recurrence or progression while being treated with this drug for this condition			
AND			
Clinical criteria			
The treatment must be commenced as neoadjuvant therapy and continued in combination with radiation therapy +/- chemotherapy after surgical resection, OR			
The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition			
AND			
Treatment criteria			
The treatment must not exceed a total of 12 cumulative months, either as (i) 17 doses (based on a 3-weekly dose regimen), (ii) 8 doses (based on a 6-weekly dose regimen) whichever comes first from the first dose of this drug regardless of if it was PBS/non-PBS subsidised			
AND			
Treatment criteria			

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

8.2 Flow on changes: amend existing pembrolizumab 'recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx' listing as follows.

Suggested additions are in italics.

MEDICINAL PRODUCT Form	**PBS item code**	**Max. Amount**	**№.of Rpts**
PEMBROLIZUMAB Injection	13131D (Public) 13114F (Private)	400 mg	6
Available brands			
Keytruda® (pembrolizumab 100 mg/4 ml injection, 4 ml vial)			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒Medical Practitioners			
Restriction type: ☒Authority Required (STREAMLINED) [13735]			
Administrative Advice: No increase in the maximum amount or number of units may be authorised.			
Administrative Advice: No increase in the maximum number of repeats may be authorised			
Administrative Advice: Special Pricing Arrangements apply			
Administrative Advice: Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.			
Restriction Summary 13734 / Treatment of Concept: 13735			
Indication: Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx			
Treatment Phase: Initial treatment			
Clinical criteria:			
The condition must be incurable by local therapies in the locally advanced setting			
AND			
Clinical criteria			
Patient must not have had systemic therapy for this condition in the recurrent or metastatic setting prior to initiating PBS-subsidised treatment with this drug for this condition			
AND			
Clinical criteria			
Patient must not have previously received programmed cell death-1/ligand 1 (PD-1/PD-L1) inhibitor therapy for any earlier stage of squamous cell carcinoma of the oral cavity, pharynx or larynx			
AND			
Clinical criteria			
Patient must not have experienced disease recurrence within 6 months of completion of systemic therapy if previously treated in the locally advanced setting			
AND			
Clinical criteria			
Patient must have had a WHO performance status of 0 or 1			
AND			
Clinical criteria:			

The treatment must be either: (i) the sole PBS-subsidised therapy where the condition expresses programmed cell death ligand 1 (PD-L1) with a combined positive score (CPS) greater than or equal to 20 in the tumour sample, (ii) in combination with platinum-based chemotherapy, unless contraindicated or not tolerated
Treatment criteria:
Patient must be undergoing treatment with this drug administered once every 3 weeks - prescribe up to 6 repeat prescriptions; or
Patient must be undergoing treatment with this drug administered once every 6 weeks - prescribe up to 3 repeat prescriptions
Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.

8.3 Flow on changes: amend existing nivolumab 'recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx' listing as follows.

Suggested additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
NIVOLUMAB Injection	11435W (Public) 11434T (Private)	480mg	8
Available brands			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)			
Restriction Summary 9283 / Treatment of Concept: 9216			
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: ☒Medical Practitioners		
	Restriction type: ☒Authority Required (STREAMLINED) [9216]		
Administrative Advice: No increase in the maximum number of repeats may be authorised			
Administrative Advice: Special Pricing Arrangements apply			
Indication: Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx			
Treatment Phase: Initial treatment			
Clinical criteria:			
Patient must have 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:			
The condition must have progressed within 6 months of the last dose of prior platinum based chemotherapy			
AND			
Clinical criteria:			
Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor for ~~this condition~~ *for any earlier stage of squamous cell carcinoma of the oral cavity, pharynx or larynx*			

	Prescribing Instructions: The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
	Prescribing Instructions: Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.
	Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.