Addendums to this Public Summary Document have been included at the end of the document.

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

1 Purpose of application

1.1 The Category 2 submission requested an Authority Required (Streamlined) listing for pembrolizumab in combination with platinum-based chemotherapy for the treatment of locally advanced (Stage III) or metastatic (Stage IV) oesophageal adenocarcinoma (OAC) or oesophageal squamous cell carcinoma (OSCC), or human epidermal growth factor receptor 2 (HER2)-negative adenocarcinoma (AC) of the gastro-oesophageal junction (GOJ).

1.2 The basis for the requested listing was a cost-utility analysis against the comparator, chemotherapy alone.

1.3 Table 1 presents the key components of the clinical issue addressed by the submission.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with Stage III unresectable (advanced)[a] or Stage IV (metastatic) OAC or OSCC, or HER2-negative[a] AC of the GOJ.
Intervention	Pembrolizumab 200 mg IV Q3W for up to 35 cycles + 5-FU 800 mg/m^2 for days 1-5 for up to 35 cycles + cisplatin 80 mg/m^2 Q3W for up to 6 cycles
Comparator	Standard of Care. Due to the complexities of the various regimens, the following have been identified and included as representative of all comparators: Cisplatin + 5-FU (represents other chemotherapy regimens including XELOX/CAPOX and FOLFOX)
Outcomes	Objective response rate, progression free survival, overall survival
Clinical claim	In patients with Stage III unresectable (advanced) or Stage IV (metastatic) oesophageal cancer or HER2 negative gastro-oesophageal junction cancer, pembrolizumab in combination with chemotherapy is more effective than standard chemotherapy at improving survival, progression free survival, and quality of life. The submission described pembrolizumab plus chemotherapy as inferior in terms of safety compared to chemotherapy alone.

Source: Table 1.1.1, pp3-4 of the submission.
AC = adenocarcinoma; 5-FU = 5 fluorouracil; FOLFOX = oxaliplatin plus leucovorin plus 5-FU; GOJ = gastro-oesophageal junction; HER2 = human epidermal growth factor receptor 2; IV = intravenous; mg = milligram; OAC = oesophageal adenocarcinoma; OSCC = oesophageal squamous cell carcinoma; Q3W = every three weeks; XELOX/CAPOX = capecitabine plus oxaliplatin
[a] The submission was inconsistent in describing the stage of disease in the target population and specifying HER2-negative status for GOJ. The restriction included advanced and metastatic, whereas the PICO table only included metastatic. This has been amended in the table.

2 Background

Registration status

2.1 Pembrolizumab was registered for OAC, OSCC or GOJ on the 28 September 2021. The TGA application for pembrolizumab for this indication was granted priority review under Project ORBIS and received a designation of Orphan Drug status. The approved TGA indication is:

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

3 Requested listing

3.1 The requested listing for pembrolizumab is provided below. Secretariat suggestions and additions proposed are shown in italics and deletions are in strikethrough.

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Pembrolizumab 100mg injection, 1 vial	200mg	6	$7,881.87 published price (private) $7,733.78 published price (public)	Keytruda, Merck Sharpe & Dohme (Australia) Pty Ltd

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: ☒Medical Practitioners
Restriction Type: ☒Authority Required (STREAMLINED)
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.*
Administrative advice: *No increase in the maximum number of repeats may be authorised.*
Administrative advice: *Special Pricing Arrangements apply.*
Episodicity: *[blank]*
Severity: *Advanced (Stage III) or metastatic (Stage IV)*
Condition: ~~Oesophageal/GOJ cancer~~ *Carcinoma of the following types: (i) Siewert type I adenocarcinoma of oesophagogastric junction, (ii) adenocarcinoma of oesophagus, (iii) squamous cell carcinoma of oesophagus*
Indication: ~~Unresectable locally advanced (III) or metastatic (IV) carcinoma of the oesophagus or HER2 negative adenocarcinoma of the gastroesophageal junction (GOJ)~~ *advanced (Stage III) or metastatic (Stage IV) carcinoma of the following types: (i) Siewert type I adenocarcinoma of oesophagogastric junction, (ii) adenocarcinoma of oesophagus, (iii) squamous cell carcinoma of oesophagus*
Treatment Phase: Initial ~~T~~*treatment*
Clinical criteria:
~~The condition must be locally advanced (Stage III) or metastatic (Stage IV) carcinoma of the oesophagus or adenocarcinoma of the gastroesophageal junction (GOJ) that is not amenable to surgical resection or definitive chemoradiation.~~ *The condition must be unsuitable for each of: (i) surgical resection, (ii) chemoradiation*
AND
~~Patient~~ *The condition* must have evidence of human epidermal growth factor receptor 2 (HER2) negativity as demonstrated

by immunohistochemistry in tumour material*, in any diagnosis of Siewert type I adenocarcinoma of oesophagogastric junction – retain this evidence on the patient's medical records; do not submit a copy of this evidence in this authority application*
AND
~~The patients should not have had prior systemic therapy administered in the metastatic setting~~
Treatment criteria:
Patient must be undergoing treatment with this drug for the first time
AND
Patient must be undergoing treatment with this drug for metastatic disease (Stage IV disease) that is untreated with drug therapy; or
~~**AND**~~
~~Patients must not have had a recurrence within 6 months of platinum-based chemotherapy in the locally advanced setting~~ *Patient must be undergoing treatment with this drug for locally advanced disease (Stage III disease) that is untreated with drug therapy*
AND
~~The treatment must be commenced in combination with platinum- and fluoropyrimidine-based chemotherapy~~
Treatment criteria:
Patient must be undergoing concomitant treatment with chemotherapy, at leas at treatment initiation with this drug, containing a minimum of: (i) a platinum agent, plus (ii) a fluoropyrimidine agent
AND
~~Patient must have a WHO performance status of 0 or 1~~ *Patient must have WHO performance status no higher than 1 at treatment initiation with this drug*
~~**Treatment criteria:**~~ ~~The treatment must not exceed a total of 7 doses under this restriction.~~
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 ~~Following completion of the initial PBS-subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.~~
Restriction Type: ☒Authority Required (STREAMLINED)
Indication: ~~Unresectable locally advanced (III) or metastatic (IV) carcinoma of the oesophagus or HER2 negative adenocarcinoma of the gastroesophageal junction (GOJ)~~ *Advanced (Stage III) or metastatic (Stage IV) carcinoma of the following types: (i) Siewert type I adenocarcinoma of oesophagogastric junction, (ii) adenocarcinoma of oesophagus, (iii) squamous cell carcinoma of oesophagus*
Treatment Phase: Continuing ~~T~~*treatment*
Clinical criteria:
~~Patient must have previously received PBS-subsidised treatment with this drug for this condition~~
~~**AND**~~
~~Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition~~
The condition must not have progressed
AND
Treatment criteria:

Patient must be undergoing continuing treatment with this drug, with PBS-subsidised treatment having commenced through one of: (i) the 'Initial treatment' phase listing, (ii) 'Grandfather arrangements' listing; do not commence PBS-subsidised treatment through this treatment phase
AND
Treatment criteria:
~~The treatment must not exceed a total of 35 cycles of treatment in a lifetime under this restriction~~.
Patient must not be undergoing continuing treatment through the PBS such that the total duration of treatment (as measured from the first dose of this drug, regardless if it was PBS-subsidised/non-PBS subsidised) goes beyond whichever comes first out of the following: (i) 24 months, (ii) 35 doses (based on a 3-weekly dose regimen), (iii) disease progression
Restriction Type: ☒ Authority Required (Streamlined)
Indication: ~~Unresectable locally advanced (III) or metastatic (IV) carcinoma of the oesophagus or HER2 negative adenocarcinoma of the gastroesophageal junction (GOJ)~~ *Advanced (Stage III) or metastatic (Stage IV) carcinoma of the following types: (i) Siewert type I adenocarcinoma of oesophagogastric junction, (ii) adenocarcinoma of oesophagus, (iii) squamous cell carcinoma of oesophagus*
Treatment Phase: ~~Grandfather Treatment~~ *Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements*
Clinical criteria:
Patient must ~~have previously received non-PBS subsidised treatment with this drug for this condition prior to~~ *be currently receiving treatment with this drug for this PBS indication, with treatment having commenced prior to* [PBS listing date]
AND
~~Patient must not have had been treated for this condition in the metastatic setting prior to initiating non-PBS subsidised treatment with this drug for this condition~~
~~**AND**~~
~~Patient must not have experienced recurrence within 6 months of completion of systemic therapy if treated in the locally advanced setting prior to non-PBS subsidised treatment with this drug for this condition~~
~~**AND**~~
~~The treatment must be commenced in combination with platinum-based chemotherapy~~
~~**AND**~~
~~Patient must have stable or responding disease~~
~~**AND**~~
~~Patient must have a WHO performance status of 0 or 1~~
Clinical criteria:
Patient must have met all other PBS eligibility criteria that a non-'Grandfather' patient would ordinarily be required to meet, meaning that at the time non-PBS supply was commenced, the patient: (i) had a WHO performance status no greater than 1, (ii) was unsuitable for both surgical resection plus chemoradiation, (iii) for a diagnosis of Siewert type I adenocarcinoma of oesophagogastric junction, there was evidence confirming HER2 negativity via immunohistochemistry in tumour material, (iv) was untreated with this drug, (v) for metastatic disease (Stage IV disease), the metastatic disease had yet to be treated with drug therapy, (vi) for locally advanced disease (Stage III disease), the locally advanced disease had yet to be treated with drug therapy, (vii) was treated concomitantly with chemotherapy containing at least each of a platinum agent plus a fluoropyrimidine agent
AND
Clinical criteria:
The condition must not have progressed

~~**AND**~~
~~**Treatment criteria:**~~
~~The treatment must not exceed a total of 35 cycles of treatment in a lifetime under this restriction.~~
Treatment criteria:
Patient must not be undergoing continuing treatment through the PBS such that the total duration of treatment (as measured from the first dose of this drug, regardless if it was PBS-subsidised/non-PBS subsidised) goes beyond whichever comes first out of the following: (i) 24 months, (ii) 35 doses (based on a 3-weekly dose regimen), (iii) disease progression
~~**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.~~ ~~A patient may only qualify for PBS-subsidised treatment under this restriction once.~~ ~~Following completion of the initial PBS subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.~~
Administrative advice: *Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.*
Administrative advice: *This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.*

3.2 The submission stated that a Special Pricing Arrangement (SPA) will be required. The submission included an ex-manufacturer price per 100 mg vial of $[redacted] and the Pre-Sub-Committee Response (PSCR) proposed a revised price of $[redacted]

3.3 The requested restriction is generally consistent with the approved TGA indication and the inclusion criteria of the KN590 trial.

3.4 HER2-negative status is only relevant to patients with AC of the GOJ. Patients with AC of the GOJ would receive a HER2 test to determine eligibility for treatment with trastuzumab (which is PBS listed for HER2-positive GOJ), but patients with OAC and OSCC may not routinely receive a HER2 test, and thus have unknown HER2 status.

3.5 The requested restriction stated: "The treatment must be commenced in combination with platinum- and fluoropyrimidine-based chemotherapy." The Secretariat suggested rewording to "Patient must be undergoing concomitant treatment with chemotherapy, at least at treatment initiation with this drug, containing a minimum of: (i) a platinum agent, plus (ii) a fluoropyrimidine agent". The PBAC considered this could be simplified to "Patient must be undergoing concomitant chemotherapy with a platinum agent plus a fluoropyrimidine agent at treatment initiation with this drug". The criterion permits use of pembrolizumab with cisplatin + 5-FU, FOLFOX, or XELOX/CAPOX (paragraph 5.2).

3.6 The PBAC considered that the restriction should reflect that a requirement for HER2 testing should only apply to patients with AC of the GOJ, and to fully align with the TGA outcome, the restriction should specify the location of the tumour centre above the junction (1 to 5 cm) by stating "Siewert type I adenocarcinoma of oesophagogastric junction" as part of the restriction condition. The PBAC considered

the restriction should specify Siewert type I GOJ cancer. The PBAC noted that even with inclusion of this wording there was a risk pembrolizumab would be used in Siewert type II and III GOJ and gastric cancer.

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

4 Population and disease

4.1 Oesophageal cancer is the eighth most common cancer and the sixth most common cause of cancer death worldwide. Squamous cell carcinoma and adenocarcinoma account for over 95 per cent of oesophageal malignant tumours (Saltzman 2021[1]). Smoking and alcohol are major risk factors for OSCC, while Barrett's oesophagus with intestinal metaplasia (a complication of gastroesophageal reflux disease), obesity, and smoking are risk factors for OAC.

4.2 In a review of all oesophageal cancer patients presented to the South Australia state-wide upper gastrointestinal cancer multi-disciplinary team from 2012 to 2014 (Nguyen 2019[2]), the diagnosis was OAC in 69.6%, OSCC in 24.8% and high grade dysplasia (HGD) in 5.6%. The majority of patients presented with Stage II and III disease (56.8%). A total of 51.5% were treated with curative intent, with 28.8% undergoing surgery and/or neoadjuvant therapy. Treatment was palliative in 48.5%, with chemoradiotherapy utilised in 20.8%.

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

5 Comparator

5.1 The submission noted that there is no single main comparator, since the choice of agent in first line is determined by the patients' performance status, organ function and the ability to swallow. There are currently three main chemotherapy regimens used in Australia and recommended by Australian Guidelines:

- Cisplatin and fluorouracil (5-FU);
- Oxaliplatin and capecitabine (XELOX/CAPOX); and

[1] Saltzman JR. Clinical manifestations, diagnosis, and staging of esophageal cancer. UptoDate. 2021 [last updated July 23, 2021].
https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-staging-of-esophageal-cancer?search=esophageal%20cancer&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

[2] Nguyen T-MN; Hummel R; Bright T; Thompson SK; Tornqvist B; Watson DI. Pattern of care for cancer of the oesophagus in a western population. ANZ J Surg 89 (2019) E15–E19.

- Leucovorin calcium (folinic acid), 5-FU and oxaliplatin (FOLFOX).

5.2 The submission stated that cisplatin + 5-FU has been selected as representative of all platinum- and 5-FU-based regimens and is therefore representative of all standard of care comparators. The submission noted that all three regimens are used in practice, with clinicians considering them to be interchangeable with respect to efficacy and safety. The PSCR stated that while FOLFOX and XELOX/CAPOX are the most commonly used regimens, the PBAC has previously deemed all platinum doublets to be comparable and clinically non-inferior (Section 6, gefitinib Public Summary Document (PSD), July 2013) and fluoropyrimidines to be interchangeable (Table 1, trastuzumab PSD, July 2015). The ESC agreed with the PSCR that most patients would receive FOLFOX or XELOX/CAPOX regimens, as they have comparable efficacy and reduced toxicity compared with cisplatin + 5-FU. The ESC agreed with the submission that cisplatin + 5-FU can be considered representative of all platinum- and 5-FU-based regimens.

5.3 The submission also noted that nivolumab plus chemotherapy may be a near term comparator. The PBAC noted that nivolumab was being considered at the same PBAC meeting for advanced or metastatic gastric cancer, GOJ cancer and OAC. The PBAC noted the indications for pembrolizumab and nivolumab (which were based on the clinical trial populations) do not fully align; however, the PBAC considered there was likely to be significant overlap in clinical practice due to overlap in anatomical distribution of these cancers.

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 an individual, health care professionals (HCPs) (2) and organisations (2) via the Consumer Comments facility on the PBS website.

6.3 The comments from two HCPs emphasised the aggressive nature of the disease and the poor prognosis for patients. One HCP stated that there is an urgent need for newer agents to be available, and commented that unlike some other cancers, there are few survivors to advocate for this patient population, as the majority of patients die within 12 months of diagnosis. Another HCP described the course of the disease where patients have simultaneous issues with metastatic cancer spread and difficulty swallowing from the primary cancer, leading to rapid weight loss, decreased quality of

life and side effects from chemotherapy. The HCP emphasised that the current options for treatment are very limited, and commented that the KEYNOTE 590 trial (along with the CheckMate 648 nivolumab trial) was one of the only positive clinical trials in oesophageal cancer for a long time.

6.4 The PBAC noted the advice received from the Pancare Foundation clarifying the likely use of pembrolizumab in clinical practice. In addition to similar issues listed in paragraph 6.3, Pancare described oesophageal carcinoma and HER-2 negative gastro-oesophageal carcinoma as having one of the worst survival rates of all cancers in Australia (5-year survival 22.5%). Pancare stated that a PBS listing for pembrolizumab would enable access to a superior first-line treatment and offer much-needed hope for Australians with oesophageal cancer. The PBAC noted that this advice was supportive of the evidence provided in the submission.

6.5 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the use of pembrolizumab in first line (1L) oesophageal carcinoma (OC) and HER2-negative AC of the GOJ, categorising it as one of the therapies of "highest priority for PBS listing" for patients with PD-L1 CPS ≥ 10% and "high priority for PBS listing" for all patients (regardless of PD-L1 CPS expression) on the basis of the KEYNOTE 590 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab (+ chemotherapy) in 1L OC and HER2-negative AC of the GOJ, which was limited to 4 (out of a maximum of 5, where 4 and 5 represent the grades with substantial improvement)[3], based on a comparison with chemotherapy alone.

6.6 One individual who has used pembrolizumab provided insight into their experience with oesophageal cancer and treatment with this medicine. The individual reported their positive experience with treatment including being able to work, a reduction in pain and weight gain. The patient advocated that access to pembrolizumab should be available through the PBS.

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

Clinical trials

6.7 The submission was based on KEYNOTE 590 (KN590) (n=749), a randomised, double blind trial comparing pembrolizumab + chemotherapy (n=373) to cisplatin + 5-FU (n=376) in patients with locally advanced unresectable or metastatic OAC or OSCC or advanced/metastatic Siewert type I AC of the GOJ. The ESC noted that 73% of patients enrolled in KN590 were diagnosed with OSCC, 15% had OAC and 12% had AC of the GOJ.

6.8 Details of the KN590 trial presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Keynote 590 (KN590)	A Phase III randomised study of chemotherapy + pembrolizumab vs chemotherapy + placebo as first-line therapy for patients with advanced oesophageal or esophagogastric junction (E/EGJ) cancer.	CSR. September 2020
	Kato K, Shah MA, Enzinger P, Bennouna J, Shen L, Adenis A, Sun JM, Cho BC, Özgüroğlu M, Kojima T, Kostorov V, Hierro C, Zhu Y, McLean LA, Shah S, Doi T. KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer.	Future Oncol. 2019 Apr;15(10):1057-1066. Epub 2019 Feb 8.
	Kato K, Sun J, Shah MA, Enzinger PC, Adenis A, Doi T, Kojima T, Metges J, Li Z, Kim S, Chul Cho BC, Mansoor W, Li S, Sunpaweravong P, Maqueda MA, Goekkurt E, Liu Q, Shah S, Bhagia P, Shen L,	Annals of Oncology (2020) 31 (suppl_4): S1142-S1215. [abstract]

Source: Table 2.2-1, p10 of the submission.

6.9 The key features of the KN590 trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Pembrolizumab plus chemo vs. chemo alone						
KN590	749	R, DB, MC ~12 mths[a]	Low	First line	OS, PFS	OS, PFS, ToT

Source: pp10-20 of the submission.

DB = double blind; MC = multi-centre; OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised; ToT = time on treatment

[a] Median follow-up in treatment arm

6.10 The dual primary efficacy outcomes for KN590 were overall survival (OS) and progression free survival (PFS). Overall Response Rate (ORR) was the key secondary efficacy endpoint.

6.11 The KN590 trial was evaluated in a stepwise fashion, with sequential hypothesis testing. This included key primary and secondary outcomes in the following pre-specified subgroup populations:

- Participants with OSCC in the intention-to-treat (ITT) population.
- Participants with OSCC with programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥10 in the ITT population (OSCC CPS ≥10).

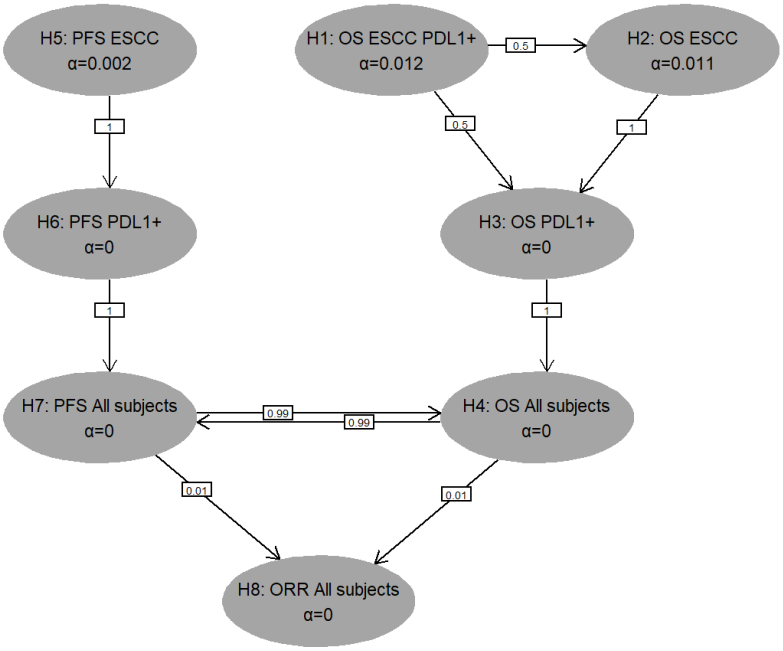
- Participants with PD-L1 CPS ≥10 in the ITT population.

6.12 Protocol Amendment 8 included the addition of three primary objectives and their corresponding hypotheses.

- OS in OSCC population.
- OS in OSCC CPS ≥10 population.
- PFS in OSCC population.

6.13 Figure 1 illustrates the sequential hypothesis testing in the KN590 trial.

Figure 1: Sequential hypothesis testing and alpha spending in the KN590 trial



Source: Figure 2.4-2, p23 of the submission.
ESCC = oesophageal squamous cell carcinoma; H = hypothesis; ORR = objective response rate; OS = Overall survival; PDL+ = programmed death-ligand 1 positive; PFS = progression free survival.

Comparative effectiveness

6.14 Key survival results of the KN590 trial are summarised in Table 4.

Table 4: Summary of ITT survival outcomes in KN590

	Pembrolizumab plus chemo N=376	Chemo alone N=376	Absolute difference	HR[b] (95% CI) p-value
Progression-free survival				
Patients with event n (%)	297 (79.6)	333 (88.6)	-	-
Median[a] PFS months (95% CI)	6.3 (6.2, 6.9)	5.8 (5.0, 6.0)	0.5 months	**0.65 (0.55, 0.76)** p-value[c] <0.0001
Proportion progression free at 12 months (95% CI)	62.4 (57.1, 67.3)	48.7 (43.4, 53.7)	13.7%	**-**
Overall survival				
Patients with event n (%)	262 (70.2)	309 (82.2)	-	-
Median[a] OS months (95% CI)	12.4 (10.5, 14.0)	9.8 (8.8, 10.8)	2.6 months	**0.73 (0.62, 0.86)** p-value[c] <0.0001
Proportion alive at 12 months (95% CI)	50.6 (45.4, 55.6)	39.4 (34.4, 44.3)	11.2%	**-**

Source: Table 2.5.2, p30 and Table 2.5.3, p32 of the submission.

Chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression free survival.

[a] Median survival was estimated through Kaplan Meier product-limit method of censored data.

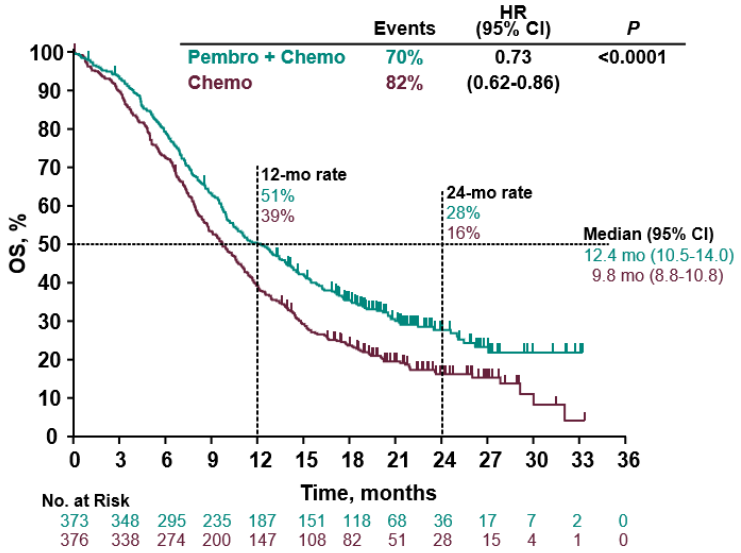
[b] Hazard ratio was based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

[c] The one-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

6.15 The KN590 results showed statistically significant improvements in both PFS and OS in the ITT population.

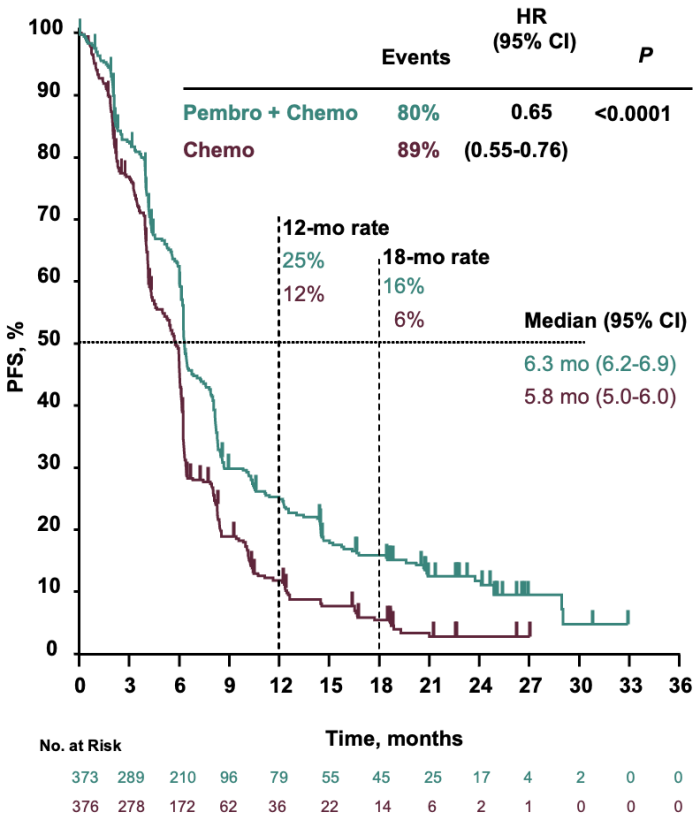
6.16 Figure 2 and Figure 3 present the KN590 Kaplan Meier survival curves for OS and PFS, respectively.

Figure 2: Kaplan-Meier Estimates of Overall Survival (ITT Population)



Source: Figure 2.5-1, p31 of the submission.
CI = confidence interval; HR = hazard ratio; mo = month; No = number; OS = overall survival

Figure 3: Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (ITT Population)



Source: Slide 9 of Kato 2020 ESMO presentation.
CI = confidence interval; HR = hazard ratio; mo = month; No = number
Note: The submission erroneously copied the OS Kaplan Meier curve for the PFS results. This was corrected in the evaluation.

6.17 Table 5 presents the subgroup results for the pre-specified KN590 primary endpoints discussed above, as well as additional exploratory analyses compiled by the FDA (including PD-L1 CPS >/< 1, and OAC patients by CPS status).

Table 5: Subgroup analyses from KN590 prespecified analyses and FDA analyses from TGA Delegate's Overview

Population	N	OS HR (CI)	P
OSCC CPS ≥10	286	0.57 (0.43, 0.75)	Significant
OSCC all CPS	548	0.72 (0.60, 0,88)	Significant
All cancer types, CPS ≥10	383	0.62 (0.49, 0.78)	Significant
All patients	749	0.73 (0.62, 0.86)	Significant
All cancer types, CPS <10 [a]	347	0.86 (0.68, 1.10)	Not tested
OSCC, CPS <10 [a]	247	0.99 (0.74, 1.32)	Not tested
OAC, CPS <10 [a]	100	0.66 (0.42, 1.04)	Not tested
CPS <1 [a]	[redacted]	[redacted]	[redacted]
CPS >1 [a]	[redacted]	[redacted]	[redacted]

Source: Page 27 of TGA Delegate's Overview

CI; = confidence interval; CPS = combined positive score; HR = hazard ratio; OAC = oesophageal adenocarcinoma; OS = overall survival; OSCC = oesophageal squamous cell carcinoma

[a] *Note that these results presented in Table 5 were not part of the pre-specified statistical plan for KN590. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.18 The KN590 trial included results of the European Organisation for Research and Treatment of Cancer Quality of Care (EORTC-QLQ) C30 questionnaire and the Oesophageal cancer module (OES18) as well as the European Quality of life 5 dimensions Visual Analogue Scale (EQ-5D VAS) as exploratory analyses. No statistically significant differences were observed in these quality of life measures.

6.19 The PBAC noted the objective response rate (ORR) for patients treated with pembrolizumab in combination with chemotherapy was 45.0% with a median duration of response of 8.3 months compared to a 29.2% ORR and a median duration of response of 6.0 months for patients treated with chemotherapy.

Comparative harms

6.20 The analysis of safety data in this study were based on the All Subjects as Treated (ASaT) population which consists of all randomised participants who received at least one dose of study treatment. Table 6 presents a summary of adverse events (AEs) in the KN590 trial.

Table 6: Summary of key adverse events in KN590 (ASaT population)

Trial	Pembrolizumab plus chemo n (%)	Chemo alone n (%)	RD (95% CI)
Subjects in population (N)	370	370	--
One or more AEs	370 (100)	368 (99.5)	0.01 (0.00, 0.02)
Drug-related† AEs	364 (98.4)	360 (97.3)	0.01 (-0.01, 0.03)
Toxicity grade 3-5 AEs	318 (85.9)	308 (83.2)	0.03 (-0.02, 0.08)
Toxicity grade 3-5 drug-related AEs	266 (71.9)	250 (67.6)	0.04 (-0.02, 0.11)
Non-serious AEs	368 (99.5)	367 (99.2)	0 (-0.01, 0.01)
Serious AEs	205 (55.4)	204 (55.1)	0 (-0.07, 0.07)
Serious drug-related AEs	117 (31.6)	97 (26.2)	0.05 (-0.01, 0.12)
Died	28 (7.6)	38 (10.3)	-0.03 (-0.07, 0.01)
Died due to a drug-related AE	9 (2.4)	5 (1.4)	0.01 (-0.01, 0.03)
Discontinued drug due to an AE	90 (24.3)	74 (20.0)	0.04 (-0.02, 0.1)
Discontinued drug due to a drug-related AE	72 (19.5)	43 (11.6)	0.08 (0.03, 0.13)
Discontinued drug due to a serious AE	58 (15.7)	47 (12.7)	0.03 (-0.02, 0.08)
Discontinued drug due to a serious drug-related AEs	38 (10.3)	17 (4.6)	0.06 (0.02, 0.09)
AEOSI[a]	95 (25.7)	43 (11.6)	0.14 (0.09, 0.20
Hypothyroidism	38 (10.3)	22 (5.9)	0.04 (0.00, 0.08)
Hyperthyroidism	19 (5.1)	2 (0.0.5)	0.05 (0.02, 0.07)
Pneumonitis	20 (5.4)	0	0.05 (0.03, 0.08)

Source: Table 2.5-12, p41, Table 2.5.14, p43, and Table 2.5.17, p47 of the submission

AE = adverse event; AEOSI = adverse event of special interest CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk

[a] Comprises adrenal insufficiency, colitis, hepatitis, hyperthyroidism, hypophysitis, hypothyroidism, infusion reactions, myositis nephritis, pancreatitis, pneumonitis, severe skin reactions thyroiditis, and type 1 diabetes mellitus.

Risk difference calculated post-hoc during the evaluation.

6.21 The submission noted that the most frequently reported AEs (defined as ≥40%) in the pembrolizumab + chemotherapy and in the chemotherapy alone arms were nausea, decreased appetite, fatigue, and constipation. These events were predominantly Grade 1 or 2 and manageable.

6.22 The submission stated that the drug-related AEs observed for participants treated with pembrolizumab + chemotherapy was generally consistent with the known safety profiles of pembrolizumab monotherapy and 5-FU/cisplatin chemotherapy.

6.23 The TGA Delegate considered that:

- "Safety results from KEYNOTE-590 demonstrate that pembrolizumab in combination with 5FU/cisplatin has a tolerable safety profile that reflects the adverse reaction profiles of the components, with no new safety concerns identified. The addition of pembrolizumab does not appear to significantly increase the toxicity of the chemotherapy backbone, taking into consideration the different lengths of treatment exposure."
- "Some patients can however experience severe and/or serious toxicity from pembrolizumab, generally due to immune related AEs."

- "Specifically, the incidence of death was similar in both treatment arms, (pneumonia being he commonest cause of death). The incidence of serious AEs was also similar in both arms, except for pneumonitis which was more common in combination arm (3.2% versus 0.3%); of note, pneumonitis is an expected immune related AE for pembrolizumab."
- "More serious drug-related AEs and discontinuations were seen for those in the pembrolizumab plus chemotherapy arm compared to the placebo plus chemotherapy arm. The incidence of AEOSI was higher in the pembrolizumab plus chemotherapy arm (compared to the placebo plus chemotherapy arm) as would be expected, with the AEOSI generally consistent with the known pembrolizumab safety profile."
- "The risks of pembrolizumab are therefore largely manageable with patient surveillance, treatment delays and supportive care in most patients, and are considered acceptable given the life-threatening nature of metastatic or locally advanced oesophageal carcinoma."

Benefits/harms

6.24 A summary of the comparative benefits and harms for pembrolizumab plus chemotherapy versus chemotherapy is presented in Table 7.

Table 7: Summary of comparative benefits and harms for pembrolizumab plus chemotherapy versus chemotherapy

	Pembro plus chemo n/N (%)	Chemo alone n/N (%)	Absolute difference	HR (95% CI)
Progression-free survival				
Progressed, n (%)	297 (79.6)	333 (88.6)	-	-
Median PFS, months (95% CI)	6.3 (6.2, 6.9)	5.8 (5.0, 6.0)	0.5 months	**0.65 (0.55, 0.76)** p-value <0.0001
Proportion progression free at 12 months (95% CI)	62.4 (57.1, 67.3)	48.7 (43.4, 53.7)	13.7%	**-**
Overall survival				
Deaths, n/N (%)	262 (70.2)	309 (82.2)	-	-
Median months OS (95% CI)	12.4 (10.5, 14.0)	9.8 (8.8, 10.8)	2.6 months	**0.73 (0.62, 0.86)** p-value < 0.0001
Proportion alive at 12 months (95% CI)	50.6 (45.4, 55.6)	39.4 (34.4, 44.3)	11.2%	**-**

Harms					
Adverse event	**Number of patients (%)**		**Event rate/ 100 patients[a]**		**Risk difference (95% CI)**
	Pembro plus chemo (N=782)	**Chemo alone (N=767)**	**Pembro plus chemo**	**Chemo alone**	
Serious drug-related AEs	117 (31.6)	97 (26.2)	32	26	0.05 (-0.01, 0.12)
Discontinuation drug due to a serious drug-related AE	38 (10.3)	17 (4.6)	10	5	0.06 (0.02, 0.09)
AEOSI	95 (25.7)	43 (11.6)	26	12	0.14 (0.09, 0.20)
Hypothyroidism	38 (10.3)	22 (5.9)	10	6	0.04 (0.00, 0.08)
Hyperthyroidism	19 (5.1)	2 (0.5)	5	1	0.05 (0.02, 0.07)
Pneumonitis	20 (5.4)	0	5	0	0.05 (0.03, 0.08)

Source: Table 2.5.2, p30, Table 2.5.3, p32 Table 2.5-12, p41, Table 2.5.14, p43, and Table 2.5.17, p47 of the submission
AE = adverse events; AEOSI = adverse event of special interest; Chemo = chemotherapy, CI = confidence interval; HR = hazard ratio; N = total participants in group; Pembro = pembrolizumab, SAE = serious adverse events
Note: Median survival was estimated through Kaplan Meier product-limit method of censored data
Note: Hazard ratio was based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
Note: The one-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1)
[a] Median duration of follow-up: of 12.6 months in pembrolizumab plus chemo arm and 9.8 months in chemotherapy alone arm.
Values in bold indicates statistically significant differences

6.25 On the basis of the KN590 trial presented by the submission, for every 100 patients treated with pembrolizumab plus chemotherapy (for a median duration of 12.6 months) instead of chemotherapy alone (for a median duration of 9.8 months):

- 12 more patients were alive at 12 months.

6.26 On the basis of the KN590 trial presented by the submission, for every 100 patients treated with pembrolizumab plus chemotherapy (for a median duration of 12.6 months) instead of chemotherapy alone (for a median duration of 9.8 months):

- Approximately 5 additional patients would experience a serious drug related AE;
- Approximately 4 additional patients would experience hypothyroidism;
- Approximately 5 additional patients would experience hyperthyroidism;
- Approximately 5 additional patients would experience pneumonitis; and
- Approximately 6 additional patients would experience discontinuation of treatment due to a serious drug related AE.

Clinical claim

6.27 The submission described pembrolizumab plus chemotherapy as superior in terms of effectiveness compared with chemotherapy alone and inferior in terms of safety compared to chemotherapy alone.

6.28 The submission stated that the claim of superior effectiveness is supported by:

- A 27% reduction in the risk of death compared to treatment with a platinum- and 5-FU based chemotherapy (OS HR=0.73 (0.62, 0.86)).
- A 35% reduction in the risk of death or disease progression compared to chemotherapy (PFS HR=0.65 (0.55, 0.76)).
- The maintenance of stable QoL in patients and manageable tolerability with AEs generally consistent and similar to those previously reported with either pembrolizumab or chemotherapy when used separately.

6.29 The evaluation and the ESC considered that overall, the claim of clinical superiority is reasonable in specific subgroups (OSCC; PD-L1 CPS ≥10), but it is likely that the efficacy of pembrolizumab is reduced in patients with PD-L1 CPS <10 when compared to those whose tumours express CPS ≥10. The proportion of PD-L1 CPS <10/≥10 is unknown for the Australian population, which may impact on the effectiveness of pembrolizumab in clinical practice.

6.30 The PSCR acknowledged that the proportion of patients with PD-L1 CPS <10/≥10 is currently unknown in the Australian population due to testing in this indication not being routine. The KN590 study was not designed and powered to compare the efficacy in participants with PD-L1 CPS <10 and was not stratified by CPS score. The PSCR stated that it is possible that the same CPS distribution is apparent in the local population as in the KN590 trial, and as the CPS <10 patients are encapsulated within the ITT population, the overall HR is representative of the potential effect and can ensure equity of access. The pre-PBAC response noted that the KN590 trial included 5 Australian sites, and maintained the ITT results would be applicable to Australian practice.

6.31 The proportion of OAC/OSCC in the KN590 trial (OAC in 15% of OC cases, OSCC in 73%

of OC cases, paragraph 6.7) is different to the Australian target population, with the OAC trial patients being substantially under-represented compared to Australian patients (OAC in 69.6% of OC cases, OSCC in 24.8% of OC cases, paragraph 4.2). The KN590 trial did not report pre-specified analyses for patients with OAC, and in the exploratory analysis, the difference between arms for OS did not reach statistical significance (HR = 0.74 (95% CI: 0.54, 1.02); noting the trial was not powered to assess statistical significance in this subgroup). The ESC noted that the proportion of patients with PD-L1 CPS ≥10 did not differ significantly between OAC (48%) and OSCC (52%) patients, and the point estimates of benefit are similar between histologies, albeit not powered for significance (Table 5: HR point estimate = 0.73 [ITT]; 0.72 [OSCC]; 0.74 [OAC]). The PBAC agreed with the ESC that differing proportions of histologies in the Australian population are unlikely to make a substantial difference to the magnitude of benefit.

6.32 The PSCR stated that an increase in median OS in the ITT population of 2.6 months (12.4 months vs. 9.8 months) is a valuable extension for patients with such a poor prognosis. The ESC and the PBAC noted the significant clinical benefit and agreed with the PSCR regarding the clinical significance of the increase in median OS.

6.33 The PBAC considered that the claim of superior comparative effectiveness was reasonable based on the statistically and clinically significant benefits of pembrolizumab with respect to OS and PFS in the KN590 trial. The PBAC noted that the treatment benefit of pembrolizumab was less in patients with PD-L1 CPS <10 (HR 0.86) compared to patients with CPS≥10 (HR 0.62) and, while the study was not powered for this comparison, there are biologically plausible reasons for this observation. The PBAC considered the magnitude of the clinical benefit in the Australian population that would be treated with pembrolizumab is uncertain due to the proportion of patients with PD-L1 CPS <10/≥10 being unknown for the Australian population.

6.34 The submission stated that, in terms of safety, analysis of the relative risk and risk difference has demonstrated that pembrolizumab in combination with chemotherapy has a higher incidence of grade 3-5 AEs than chemotherapy indicating that the safety profile is inferior to that of chemotherapy. The submission quoted the TGA Delegate's Overview: "The risks of pembrolizumab are therefore largely manageable with patient surveillance, treatment delays and supportive care in most patients, and are considered acceptable given the life-threatening nature of metastatic or locally advanced oesophageal carcinoma."

6.35 The PBAC agreed with the ESC, that the claim of inferior safety was reasonable and considered the additional toxicity (hyper-/hypothyroidism and pneumonitis) was manageable.

Economic analysis

6.36 The submission presented a cost-utility analysis comparing pembrolizumab plus chemotherapy versus chemotherapy alone (cisplatin plus 5-FU). The submission did not present a stepped economic analysis and did not justify this omission. A summary of the model structure in the submission's economic evaluation is presented in Table 8.

Table 8: Key components of the economic evaluation

Component	Description
Type of analysis	Cost effectiveness analysis (Cost-utility analysis base case)
Outcomes	Quality-adjusted life years (QALY; base case), Life-years (LY; sensitivity analysis) gained
Time horizon	7.5 years in the model base case based on a median follow up of 9.8 and 12.6 months in the chemotherapy and pembrolizumab plus chemotherapy arms of the KN590 trial, respectively.
Methods used to generate results	Cohort analysis of partitioned survival (i.e., area under the curve)
Health states	Three health states are included in the model: PFS, progressed disease and death
Cycle length	1 week
Transition probabilities	Health state allocation over time was determined by PFS and OS curves from the KN590 trial (partitioned survival analysis)
Extrapolation method	Piecewise (models for all extrapolations) *OS:* KM data up to 40 weeks, and then log-logistic for pembrolizumab plus chemo arm and log-normal for chemotherapy alone arm. *PFS:* KM data up to 37 weeks, then exponential for pembrolizumab plus chemo and for chemotherapy alone KM data only for time on treatment as all treatment curves reached zero before end of trial. The model is highly sensitive to choice of extrapolation.
Health related quality of life	Progression free (0.811) and progressed (0.696) based on KN590 trial based EQ-5D responses.[a]
Inclusion of terminal care costs	$77,018.71 based on Goldsbury (2018) and adjusted for 2020 prices. May not be reflective of requested population, highly linked to extrapolation of OS benefit. May not be reasonable to include terminal care costs where survival is not expected to surpass the modelled time horizon. The PSCR provided a revised terminal care cost of $38,057.

Source: Table 3.1-1, p 61 of the submission.
LY life year; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life year
[a] The Pre-Sub-Committee Response (PSCR) provided additional information on the derivation of the health utilities. The utilities were first cross walked to EQ-5D-3L and then mapped to Australia specific utilities.

6.37 The ESC noted a key limitation of the model is the applicability of the KN590 data on which it is based, as it was unclear how applicable the trial was to the Australian population (as discussed in paragraph 6.33).

6.38 The model's extrapolation method was explicitly selected to demonstrate a survival plateau effect of pembrolizumab. The evaluation noted the Advisory Committee Medicines (ACM) spoke positively of the long tail in survival for a subset of patients (ACM Minutes). The submission stated that single-piece models generated poorly

fitting extrapolations of the data and that this is consistent with the findings of previous independent immuno-oncology (IO) validation studies that have shown that single-piece parametric functions underestimate empirically measured survival data for these therapies (Bullement 2019; Phan 2020; Ouwens 2019) as they inadequately represent the complex pattern of hazard functions or underlying mechanism of action of IO treatments (Ouwens 2019).

6.39 The submission considered that the use of more flexible approaches to extrapolation is in line with current academic thinking both in analogous HTA markets (NICE DSU paper 21 2020) and Australian academics (Gray J, Sullivan T, Latimer NR et al 2021). It has also been suggested by the ESC in recent appraisals (darolutamide in July 2020; pembrolizumab in November 2020). The ESC noted that the sources referenced specifically refer to the use of flexible parametric models and cure models (where an assumption of a meaningful cured proportion is supported by the clinical evidence). The ESC noted an assumption underpinning the use of piecewise models is that the data within each section is sufficient for robust survival modelling (NICE DSU paper 21, 2020). The ESC noted that a piecewise extrapolation with a 40 week cut-off results in additional weight being attached to the tail of the Kaplan-Meier data i.e., the extrapolation is more sensitive to survival data informed by low patient numbers.

6.40 The submission stated a piecewise approach was selected to represent an assumed plateau in survival. However, ESC considered modelling a survival plateau may not be supported by the clinical evidence presented in the submission. The ESC noted the assumption of a plateau in survival was based on observation of the KM curve (Figure 2) when only a small number of patients remain at risk. The ESC considered the piecewise approach may not be reasonable as it modelled a survival plateau which may not be realised in clinical practice. The piecewise approach in the base case (40 week cut-off) estimated a larger increment in overall survival (0.57 life years, undiscounted) compared to the one-piece approach (0.46 life years, undiscounted). The ESC considered the one-piece approach, in which survival models are fitted to the full data and a parametric model is used to extrapolate from Week 98, was a more appropriate, conservative method. The ESC noted using a one-piece approach, extrapolating from Week 98 with the best fitting function (log-logistic according to AIC and BIC for pembrolizumab + chemotherapy and chemotherapy alone for OS and progression free survival [PFS]), rather than the piecewise model, increased the ICER from $95,000 to < $115,000/QALY in the base case to $115,000 to < $135,000/QALY. The ESC noted the revised extrapolation predicted survival differences at 7.5 years, which may still be optimistic.

6.41 The PSCR justified using a cut-off point of 40 weeks for piecewise model fitting as being in line with the peak of the Chow test for OS in the pembrolizumab + chemotherapy arm. The PSCR stated that while the peak for the OS Chow test for the chemotherapy

arm occurs at a later time point (i.e. after week 100); the Kaplan-Meier event data after this time point are too sparse to be used for parametric fitting.

6.42 The pre-PBAC response acknowledged that while the Sponsor considered the piecewise extrapolation method to be the most appropriate approach to accurately capture the long-term benefits of immunotherapies, other extrapolation methods such as a one-piece approach, extrapolating from Week 98 with appropriate functions applied, may also account for the survival plateau seen with immunotherapies.

6.43 The submission applied terminal care costs of approximately $77,000 (Goldsbury 2018) to the death state in the model. The estimate was specific to terminal phase of head and neck cancers, which was the highest of all of the 11 cancer types of terminal care cost estimates. No costs were included specific to oesophageal cancer. Goldsbury (2018) defined the cost of terminal phase care as all costs in the final year up to and including the death date. This, consequently, would likely constitute mostly double counted costs, as median survival in KN590 ITT population was 12.4 months for pembrolizumab plus chemotherapy and 9.8 months in the chemotherapy alone arm. The PSCR proposed a revised terminal care cost of $38,057 based on an estimate from Langton 2016 converted to 2021 prices. The ESC noted the Langton paper estimated that elderly patients with a variety of different types of cancers who died of cancer accrued $30,001 of costs in the last six months of life. The PSCR response reduced the price of pembrolizumab (from $[redacted]/vial to $[redacted]/vial) to maintain an ICER of $95,000 to < $115,000/ QALY using the revised terminal care cost.

6.44 Given that few patients would be expected to survive beyond 7.5 years, and there is no indication-specific clinical evidence to support that pembrolizumab plus chemotherapy would improve survival in the long term, and the issues with the cost estimate itself, it is likely more reasonable to assume that there would be no difference in terminal care costs between the treatment arms. Moreover, it is likely that treatment with pembrolizumab plus chemotherapy delays, rather than prevents, incurring terminal care costs in the proposed PBS population. Removing the cost of terminal care increased the ICER substantially. The ESC noted the impact of including terminal care costs on the ICER is driven by the difference in surviving proportions at the end of the model time horizon but ultimately this cost should accrue to all patients in both treatment arms. Additionally, the ESC noted the terminal care cost was based on the 12 months prior to death and considered this may result in double counting as some of these costs would have accrued in the progressed health state. The ESC noted excluding terminal care costs increased the ICER from $95,000 to < $115,000/QALY gained to $95,000 to < $115,000/QALY gained (based on the price proposed in the submission).

6.45 Key drivers of the model are presented in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact (Base case ICER: [redacted][1])
Extrapolation	Piecewise extrapolations. OS: KM data up to 40 weeks, and then log-logistic for pembrolizumab plus chemo arm and log-normal for chemotherapy alone arm. PFS: KM data up to 37 weeks, then exponential for pembrolizumab plus chemo and for chemotherapy alone	High, favours pembrolizumab. Using KM data to Week 98, then a one-piece with the best fitting function (log-logistic according to AIC and BIC for pembrolizumab + chemotherapy and chemotherapy alone for OS and PFS) rather than piecewise models, leads to an ICER of [redacted][2].
Time horizon	7.5 years	High, likely favours pembrolizumab. Reducing time horizon to 5 years increases ICER to [redacted][2]. The ESC considered a 7.5 year time horizon may be optimistic for this population.
Terminal care costs	Cost of $77,019 added to death state based on Goldsbury (2018). The PSCR provided a revised terminal care cost of $38,057.	High, favours pembrolizumab. Removing terminal care costs increases the ICER to [redacted][1]. Using the revised terminal care cost resulted in an ICER of [redacted][1].

Source: pp99-102 of the submission.
ICER = incremental cost effectiveness ratio; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival; PSCR = Pre-Sub-Committee Response.
The redacted values correspond to the following ranges:
[1] $95,000 to < $115,000[2] $115,000 to < $135,000

6.46 Model results are presented in Table 10.

Table 10: Results of the economic evaluation

Component	Pembrolizumab plus chemo	Chemotherapy alone	Increment
Costs ($)	[redacted]	$79,712	[redacted]
Lys	1.7102	1.2245	0.4857
QALYs	1.2858	0.9147	0.3711
Incremental cost/extra LY gained			[redacted][1]
Incremental cost/extra QALY gained			[redacted][2]

Source: Table 3.8-3, p98 and table 3.8-4, p99 of the submission.
Chemo = chemotherapy; LY = life year; QALY = quality adjusted life year.
The redacted values correspond to the following ranges:
[1] $55,000 to < $75,000
[2] $95,000 to < $115,000

6.47 Sensitivity analyses for the economic evaluation are presented in Table 11.

Table 11: Results of sensitivity analyses (based on pembrolizumab price proposed in the submission)

Analyses			Incremental cost ($)	Incremental QALY	ICER
Base case			[redacted]	0.37	[redacted]1
Trial population (ITT in BC)	OSCC		[redacted]	0.41	[redacted]2
	PD-L1+ (CPS ≥10)		[redacted]	0.53	[redacted]3
	OSCC and PD-L1+ (CPS ≥10)		[redacted]	0.61	[redacted]3
Discount rate (5% in BC)	0%		[redacted]	0.43	[redacted]2
	3.5%		[redacted]	0.39	[redacted]2
Time horizon (7.5 years in BC)	5 years		[redacted]	0.30	[redacted]5
	10 years		[redacted]	0.42	[redacted]2
Terminal care costs	Removed		[redacted]	0.37	[redacted]1
	Revised cost provided in PSCR		[redacted]	0.37	[redacted]4
No relative dose intensity applied for 1L treatments			[redacted]	0.37	[redacted]4
Time to death utility approach rather than progression based			[redacted]	0.42	[redacted]2
Utility increment for treatment			[redacted]	0.40	[redacted]2
Market share for blended comparator (100% 5-FU + cisplatin in BC)	Assumed equal market share (12.5%) across chemotherapy arm and blended chemotherapy comparators		[redacted]	0.37	[redacted]2
	Assumed 50%/50% CAPOX/FOLFOX		[redacted]	0.37	[redacted]2
	Assumed 80%/20% FOLFOX/ CAPOX		[redacted]	0.37	[redacted]2
Apply OS waning effect for pembrolizumab + chemotherapy (OS converges)			[redacted]	0.37	[redacted]4
Extrapolation					
Pembrolizumab + chemotherapy and chemo alone: Use Week 32 piecewise with the best fitting function (log-logistic for pembrolizumab + chemotherapy and Gompertz for chemo alone according to AIC and BIC) for OS rather than Week 40 piecewise			[redacted]	0.35	[redacted]4
Pembrolizumab + chemotherapy and chemo alone for OS and PFS: Use Week 98 one-piece with the best fitting function (log-logistic according to AIC and BIC for pembrolizumab + chemotherapy and chemo alone for OS and PFS) rather than piecewise models			[redacted]	0.31	[redacted]5
Multivariate analyses					
Use Week 98 one-piece with the best fitting function (log-logistic according to AIC and BIC for pembrolizumab + chemotherapy and chemo alone for OS and PFS)		And remove terminal care costs	[redacted]	0.31	[redacted]5
Use Week 98 one-piece with the best fitting function (log-logistic according to AIC and BIC for pembrolizumab + chemotherapy and chemo alone for OS and PFS)		Revised terminal care costs in PSCR	[redacted]	0.31	[redacted]5
Use Week 98 one-piece with the best fitting function (log-logistic according to AIC and BIC for pembrolizumab + chemotherapy and chemo alone for OS and PFS)	And remove terminal care costs	5 year time horizon	[redacted]	0.27	[redacted]6

Source: 3.9-1, pp101-102 of the submission.

AIC = Akaike Information Criteria; BC = base case; BIC = Bayesian Information Criteria; CPS = combined positive score; 5-FU = 5-fluorouracil; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; OSCC = oesophageal squamous cell carcinoma; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression free survival; PSCR = pre-sub-committee response; QALY = *quality adjusted life year*.

The redacted values correspond to the following ranges:

[1] *$95,000 to < $115,000*
[2] *$75,000 to < $95,000*
[3] *$55,000 to < $75,000*
[4] *$95,000 to < $115,000*
[5] *$115,000 to < $135,000*
[6] *$135,000 to < $155,000*

6.48 The ESC noted the multivariate analysis that (i) used the Week 98 one-piece with the best fitting function (log-logistic according to AIC and BIC for pembrolizumab + chemotherapy and chemo alone for OS and PFS) and (ii) removed the terminal care costs resulted in an ICER of $115,000 to < $135,000/QALY gained. The ESC considered this scenario may provide a more reasonable base case, noting the predicted survival differences at 7.5 years may still be optimistic. The ESC noted applying a 5 year time horizon increased the ICER from $115,000 to < $135,000/QALY to $135,000 to < $155,000/QALY. The PBAC noted that applying the revised price proposed in the PSCR resulted in ICERs of $115,000 to < $135,000/QALY (7.5 year time horizon) and $135,000 to < $155,000/QALY (5 year time horizon).

6.49 The pre-PBAC response stated that:

- The 7.5 year time horizon within the alternative ESC base case adequately captures the benefits in those patients who have a complete response and who have a longer-term benefit.
- The terminal care costs should not be excluded. The Sponsor maintained that the revised costs based on the publication by Langton et al. 2016 should be used in the economic model.
- The application of a Week 98 one-piece curve may be appropriate as a more conservative method, provided the appropriate survival functions are applied to each arm. The Sponsor agreed with the ESC advice of applying a log-logistic function to the pembrolizumab + chemotherapy arm, as it is representative of the survival plateau seen with immunotherapies in oesophageal cancer and other cancer types, but commented that the application of a log-logistic function to the standard of care arm would result in a greater proportion of patients alive than is clinically plausible. The Sponsor noted that only a very small number of patients receiving chemotherapy would typically be alive at 2-3 years, with none surviving greater than 5 years.

Drug cost/patient/course $[redacted] to $[redacted]

6.50 The submission calculated the average cost per patient of pembrolizumab accrued in the economic evaluation. This was calculated by multiplying the DPMQ of pembrolizumab times the KN590 relative dose intensity and estimating the total cost per treatment using the time on treatment survival analysis. During the evaluation, this method of calculating treatment cost was applied to the chemotherapy

components of the proposed regimen, cisplatin plus 5-FU and that of the comparator as well.

6.51 Drug costs per patient are presented in Table 12.

Table 12: Drug cost per patient for pembrolizumab and chemotherapy

Drug and dose	Cost per cycle			Number of cycles			Total cost per course		
	Model[a]	KN590[a]	Financials	Model[b]	KN590	Financial	Model	KN590	Financials
Pembrolizumab plus cisplatin plus 5-FU									
Pembrolizumab	$		$	11.7	11.0	10.96	$	$	$
Cisplatin	$83.62		Not included	4.79	4.7	Not included	$400.63	$393.01	Not included
5-FU	$115.41			8.73	8.0		$1,007.99	$923.28	
Total							**$**	**$**	$
Chemotherapy alone									
Cisplatin	$93.68		Not included	4.69	4.7	Not included	$439.26	$440.30	Not included
5-FU	$123.61			7.60	7.1		$938.83	$877.63	
Total							**$1,378.10**	**$1,317.93**	

Source: Table 14.1-35, p339 of the KN590 CSR; 'Drug Costs' worksheet of "Sec 3 Workbook" attached to submission.

Note: small discrepancies between presented results and products of their presented factors are due to rounding.

[a] cost per cycle includes adjustment with trial based relative dose intensity: as follows, 93.4% for pembrolizumab, 71.8% for 5-FU in the treatment arm, and 58.2% for cisplatin in the treatment arm, 76.9% for 5-FU in the control arm, and 65.2% for cisplatin in the control arm.

[b] Cycles of treatment back-calculated in the model by dividing undiscounted total cost of treatment by the dose adjusted cost per cycle of treatment

Estimated PBS usage & financial implications

6.52 This submission was considered by DUSC.

6.53 The submission took an epidemiological approach to estimate use and financial impact.

6.54 A summary of inputs and their data sources are presented in Table 13.

Table 13: Data sources and inputs in the financial estimates

Data	Value	Source	Comment
Eligible population			
Incident patients with oesophageal cancer	[redacted][1] in Year 1	AIHW (2018) With growth based on average historical growth rate between 2010 and 2021	Yearly growth of 1.4%. The DUSC noted GOJ patients would not be included in this estimate and considered that Siewert Type I GOJ AC patients should be explicitly included in the financial estimates
Prevalent patients with oesophageal cancer	[redacted][1] in Year 1	AIHW (2018)	Yearly growth of 1.4%. The DUSC noted GOJ patients would not be included in this estimate and considered that Siewert Type I GOJ AC patients should be explicitly included in the financial estimates.
Proportion of incidence cases that is adenocarcinoma	74%	Nguyen (2019)	Reasonable.

Data	Value	Source	Comment
Proportion of patients with Siewert type I AC of the GOJ who are HER2+	5%	Based on Expert opinion	The submission only stated that this was based on "KSL advice" and no further details of this opinion were presented.
Stage	Stage I: 16% Stage II/III: 57% Stage IV: 27%	Nguyen (2019)	Reasonable, although this groups Stages II/III together, which may overestimate the incident population.
Proportion resectable	64%	Nguyen 2019: Proportion of patients treated with curative intent	
ECOG PS 0-1	80%	Expert opinion	The submission only stated that this was based on "KSL advice" and no further details of this opinion were presented.
Uptake	90%	Assumption	Could potentially be lower in the Australian treatment population.
Treatment utilisation			
Pembrolizumab administrations per patient dispensed	10.96 per patient	11.73 x 93.4% dose intensity	Consistent with economic model.
Costs			
Chemotherapy	Not included in submission	--	The submission stated that because pembrolizumab will be used adjunctively to platinum + 5-FU, the current comparator, no estimated change in use of other therapies was considered and so this was not included. If the claim of improved OS and PFS is accepted, this would lead to longer concomitant use of chemotherapy and thus the omission of these costs underestimates costs associated with listing pembrolizumab.

Source: pp102-113. AC = adenocarcinoma; AIHW = Australian Institute for Health and Welfare; ECOG PS = Eastern Cooperative Oncology Group Performance Status; 5-FU = 5-fluorouracil; GOJ = gastro-oesophageal junction; HER2+ = human epidermal growth factor receptor 2 positive; MBS = Medicare Benefits Schedule; OS = overall survival; PFS = progression free survival.
The redacted values correspond to the following ranges:
[1] 500 < 5,000

6.55 The submission estimated the expected population by calculating patients in four separate treatment pathways:

- Incident patients Stage III unresectable/ Stage IV patients at diagnosis.
- Patients recurrent from Stage I and II/III resectable.
- Prevalent patients.
- Grandfathered patients.

6.56 The DUSC considered that, overall, the approach to estimating the number of eligible patients using the four separate treatment pathways was reasonable. The DUSC noted that the epidemiological estimate of the eligible population excluded Siewert Type I GOJ AC patients, resulting in an underestimate of usage and financial implications.

6.57 The pre-PBAC response accepted the advice by the DUSC that the epidemiological approach to the financial estimates only included the incidence of oesophageal cancer (ICD-10 code C15) and neglected to include the incidence of GOJ adenocarcinoma which is captured under gastric cancer (ICD-10 code C16). The pre-PBAC response stated there is a lack of published data that identifies the proportion of GOJ adenocarcinoma, and the Siewert type classification is not consistent across clinical practice with some clinicians referring to Siewert type 1 as distal oesophageal cancer, and Siewert type II-III as gastric cancer. The pre-PBAC response presented revised estimates to capture the incidence of GOJ AC, based on the following assumptions:

- GOJ patients account for approximately 50% of all gastric cancer patients, based on clinician advice.
- 23-40% of GOJ adenocarcinoma patients are Siewert type 1, based on published literature (midpoint of 30% used, based on clinician advice).
- The proportion of HER2-negative patients was appropriately applied to the GOJ AC population (rather than to the oesophageal population as applied in the submission).

6.58 Estimated use and financial implications, including the revised estimates, are presented in Table 14.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated[a]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Number of scripts dispensed[b]	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Estimated financial implications for other medicines: None.						
Net financial implications						
Net cost to PBS/RPBS	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Net cost to MBS[c]	[redacted]5	[redacted]5	[redacted]5	[redacted]5	[redacted]5	[redacted]5
Net cost to Government	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Revised estimates in the pre-PBAC response						
Number of patients treated	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Net cost to PBS/RPBS[d]	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4

[a] Estimate includes < 500 grandfathered patients.
[b] Assuming 10.96 scripts per year as estimated by the submission.
[c] MBS 13950 applied.
[d] The effective vial price for pembrolizumab reduced from $[redacted]/vial to $[redacted]/vial in the PSCR. The new price was applied to the revised estimates in the pre-PBAC response.
Source: Table 4.2-7, p107, Table 4.2-9, p109, Table 4.2-16, pp110-112, and Table 4.4-1, p112, and Table 4.5-3-p113 of the submission.
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; PSCR = Pre-Sub-Committee Response.
The redacted values correspond to the following ranges:
[1] 500 to < 5,000
[2] 5,000 to < 10,000
[3] $20 million to < $30 million
[4] $30 million to < $40 million
[5] $0 to < $10 million

6.59 The total net cost to the PBS/RPBS was estimated at $20M to < $30M in Year 1, decreasing to $20M to < $30M in Year 2, before increasing back to $20M to < $30M in Year 6. The Sponsor's revised total net cost to the PBS/RPBS, capturing GOJ AC patients, was estimated at $30M to < $40M in Year 1, decreasing to $30M to < $40M in Year 2, before increasing to $30M to < $40M in Year 6.

6.60 The PBAC considered there was a high risk of pembrolizumab being used in patients with Siewert Type II or Type III AC of the GOJ and gastric cancer. Additionally, the PBAC noted there would be an impact on utilisation and financial estimates should nivolumab be recommended for PBS listing in a similar population.

Quality Use of Medicines

6.61 The submission outlined a number of activities intended to promote safe and effective use of pembrolizumab in clinical practice. These include the development of materials about how to identify and manage potential treatment-related AEs in particular immune-related AEs, as well as education activities and a 1-800 medical information service.

Financial Management – Risk Sharing Arrangements

6.62 The submission stated that the Sponsor is willing to enter into an RSA with the Commonwealth on sharing the costs of the Commonwealth subsidy for supply of pembrolizumab for the treatment of recurrent or metastatic OC and GOJA, in order to manage any risk to the overall cost to the PBS.

6.63 For the purpose of the RSA, the sponsor agrees to reimburse the Commonwealth with a proportion of the treatment costs of pembrolizumab, should use exceed the subsidisation cap in that year. Following a positive recommendation, the submission stated that the sponsor is committed to working with the Commonwealth to finalise the specific parameters for inclusion in the RSA including the rebate proportion to be paid.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of pembrolizumab in combination with chemotherapy for the treatment of locally advanced (Stage III) or metastatic (Stage IV) oesophageal adenocarcinoma (OAC) or oesophageal squamous cell carcinoma (OSCC), or human epidermal growth factor receptor 2 (HER2)-negative adenocarcinoma (AC) of the gastro-oesophageal junction (GOJ). The PBAC noted that the clinical need for effective treatments in this therapeutic area is high, given the poor prognosis for patients and the poor efficacy and high toxicity of current treatments. The PBAC considered the evidence presented demonstrated treatment with pembrolizumab resulted in a clinically meaningful improvement in progression free survival (PFS) and overall survival (OS). However, the PBAC considered the incremental cost-effectiveness ratio (ICER) in this setting at the proposed price was high and moderately uncertain.

7.2 The PBAC noted the consumer input supported the high clinical need for additional effective treatment options for this population.

7.3 The submission nominated chemotherapy alone, represented by cisplatin + 5-FU-based regimens, as the comparator. The PBAC noted nivolumab plus chemotherapy was considered at the same PBAC meeting and agreed with the submission that it is a

near-market comparator given the overlap in patient populations.

7.4 The PBAC was satisfied that pembrolizumab provided, for some patients, a significant improvement in efficacy over the nominated comparator of chemotherapy (cisplatin + 5-FU). The PBAC noted that this combination could be considered representative of all platinum- and 5-FU-based regimens, including the commonly used FOLFOX and XELOX/CAPOX regimens.

7.5 The PBAC noted that the TGA indication and trial population for pembrolizumab reflected a subset of the full patient population likely to be considered clinically appropriate for checkpoint inhibitor treatment. The PBAC indicated its preference for an aligned, simpler restriction for checkpoint inhibitors that reflected likely clinical practice across gastric, GOJ and oesophageal cancers, while noting the different TGA indications.

7.6 The submission was based on one head-to-head randomised, phase 3, double-blind multi-centre trial (Keynote 590 [KN590]; N=749) comparing pembrolizumab + chemotherapy to cisplatin + 5-FU, in patients with locally advanced unresectable or metastatic OAC or OSCC or advanced/metastatic Siewert type 1 AC of the GOJ. The PBAC noted that there was a statistically significant OS benefit associated with pembrolizumab (HR=0.73, 95% CI: 0.62, 0.86) with the median survival improving from 9.8 to 12.4 months and an improvement in PFS (5.8 months to 6.3 months, HR=0.65, 95% CI: 0.55, 0.76). The PBAC considered that the extent of OS benefit was clinically meaningful in the context of the poor prognosis of this patient population. The PBAC noted the OS benefit in patients treated with pembrolizumab compared to chemotherapy alone was supported by a higher ORR, longer duration of response and maintenance of QoL.

7.7 While the PBAC acknowledged the clinically relevant improvement in PFS and OS with pembrolizumab in the KN590 trial, it considered the magnitude of the benefit in the Australian population to be uncertain. It noted the benefit of pembrolizumab is less in patients with PD-L1 CPS <10 and the proportion of patients with CPS<10 in the Australian population was unknown. The PBAC noted that while the proportions of the OAC/OSCC histologies differed in the KN590 trial compared with the Australian population, it was unlikely to make a substantial difference to the magnitude of the benefit from pembrolizumab.

7.8 The PBAC noted that pembrolizumab in combination with chemotherapy had a higher incidence of grade 3-5 AEs than chemotherapy alone, indicating that the safety profile is inferior to that of chemotherapy. The PBAC considered that the claim of inferior safety was reasonable, and that the additional toxicity (hyper-/hypothyroidism and pneumonitis) was manageable.

7.9 The PBAC noted the base case ICER presented in the submission was $95,000 to < $115,000 per QALY gained. The PBAC considered this ICER to be high and moderately

uncertain, with the economic model sensitive to time horizon, method of extrapolation and the inclusion of terminal care costs.

7.10 The time horizon in the base case economic model in the submission was 7.5 years. The PBAC considered a 7.5 year time horizon was optimistic and a 5 year time horizon would be preferable given the median duration of follow up in KN590 was 9.8 months and 12.6 months in the chemotherapy and pembrolizumab arms, respectively, and the poor prognosis of the patient population. However, the PBAC noted it had previously recommended a 5 year time horizon in the second-line treatment setting for a similar patient population and considered a 7.5 year time horizon may be reasonable, given the earlier treatment setting, if other model assumptions were conservative.

7.11 The economic model in the submission extrapolated OS and PFS using a two-piece extrapolation method using KM data up to 40 weeks (OS) or 37 weeks (PFS) and then a log-logistic function for pembrolizumab and log-normal for chemotherapy alone for OS, and an exponential function for both pembrolizumab and chemotherapy alone for PFS. The PBAC agreed with the ESC that the use of a two-piece extrapolation method resulted in additional weight being attached to the tail of the Kaplan-Meier data (where patient numbers are low and the data is less reliable) and that a one-piece extrapolation method fitted to the full KM curve was more reliable. The PBAC noted the ESC preferred approach was a one-piece extrapolation from Week 98 with the best fitting function (log-logistic for pembrolizumab and chemotherapy alone for OS and PFS). The PBAC noted the pre-PBAC response accepted this approach was appropriate for the pembrolizumab arm as it resulted in some plateauing of survival but did not consider it appropriate for the chemotherapy arm as it may overestimate survival. The PBAC agreed with the pre-PBAC response but noted the pre-PBAC response did not propose an alternative extrapolation method for the chemotherapy arm.

7.12 The economic model in the submission applied a terminal care cost of $77,000 (reduced to $38,057 in the PSCR) to the death health state. The PBAC noted the ESC consideration of the inclusion of terminal care costs (paragraphs 6.43 and 6.44) and agreed with the ESC that terminal care costs should be excluded from the economic model.

7.13 The PBAC noted the revised financial estimates provided with the pre-PBAC response addressed the exclusion of patients with AC of the GOJ in the financial estimates (which was the main issue raised by the DUSC). However, the PBAC considered it was uncertain whether the assumptions applied were reasonable (in particular, whether GOJ cancer accounts for 50% of gastric cancer and whether 30% of GOJ cancer patients are Type I Siewert). The PBAC considered this could be further addressed in a resubmission, noting the PBAC preference for an aligned restriction across all gastric, GOJ and oesophageal cancers (see paragraph 7.6), the high risk of use of pembrolizumab outside of Type 1 Siewert GOJ (see paragraph 3.7) and the likely

overlap in patient populations for checkpoint inhibitors (see paragraph 5.3).

7.14 The PBAC noted that the Sponsor is willing to enter into an RSA with the Commonwealth on sharing the costs in order to manage any risk to the overall cost to the PBS.

7.15 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for pembrolizumab. The PBAC also considered pembrolizumab addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy over any alternative therapies. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.

- Provide an economic model based on (i) a 7.5 year time horizon (ii) one-piece extrapolation from Week 98 using the log-logistic function for OS and PFS for the pembrolizumab treatment arm and an appropriate function for the chemotherapy alone treatment arm and (iii) exclusion of terminal care costs.
- Propose a price reduction to achieve an ICER of $55,000 to < $75,000 to $75,000 to < $95,000/ QALY;
- Provide revised financial estimates based on the Section 4 model included with the pre-PBAC response, incorporating the revised price and addressing the issues raised in paragraph 7.14;
- Propose an appropriate RSA to manage the risk of use outside the proposed patient population included in the resubmission.

The early resolution resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early resolution timing is not acceptable, a standard re-entry pathway is available

7.16 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

Addendum to the November 2021 PBAC Public Summary Document:

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

8 Background

8.1 An early resolution resubmission was provided that sought to address the PBAC's concerns from its November 2021 meeting, at which the Committee did not recommend pembrolizumab in combination with chemotherapy for the treatment of treatment of advanced or metastatic oesophageal adenocarcinoma (OAC) or oesophageal squamous cell carcinoma (OSCC), or human epidermal growth factor receptor 2 (HER2)-negative adenocarcinoma (AC) of the gastro-oesophageal junction (GOJ).

Previous PBAC consideration

8.2 In November 2021, the PBAC considered a resubmission via an early resolution pathway would be acceptable if the changes outlined in paragraph 7.15 were addressed. In summary, the resubmission was required to address the following outstanding issues:

- Provide a revised economic model with a price reduction to achieve an incremental cost effectiveness ratio (ICER) of $55,000 to < $75,000 to $75,000 to < $95,000/ QALY;
- Provide revised financial estimates; and
- Propose a risk sharing arrangement that manages the risk of use outside the proposed patient population.

9 Requested listing

9.1 The requested listing is provided below. The proposed criteria incorporated changes suggested previously (see Section 3 above) with some amendments (included in italics).

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Pembrolizumab 100mg injection, 1 vial	200mg	6	$7,881.87 published price (private) $7,733.78 published price (public)	Keytruda, Merck Sharpe & Dohme (Australia) Pty Ltd

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: ☒ Medical Practitioners
Restriction Type: ☒ Authority Required (STREAMLINED)
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.
Administrative advice: No increase in the maximum number of repeats may be authorised.
Administrative advice: Special Pricing Arrangements apply.
Episodicity: [blank]
Severity: Advanced (Stage III) or metastatic (Stage IV)
Condition: Carcinoma of the following types: (i) Siewert type I adenocarcinoma of oesophagogastric junction, (ii) adenocarcinoma of oesophagus, (iii) squamous cell carcinoma of oesophagus
Indication: Advanced (Stage III) or metastatic (Stage IV) carcinoma of the following types: (i) Siewert type I adenocarcinoma of oesophagogastric junction, (ii) adenocarcinoma of oesophagus, (iii) squamous cell carcinoma of oesophagus
Treatment Phase: Initial treatment
Clinical criteria:
The condition must be unsuitable for *either*: (i) surgical resection, *or* (ii) chemoradiation
AND
The condition must have evidence of human epidermal growth factor receptor 2 (HER2) negativity as demonstrated by immunohistochemistry in tumour material, in any diagnosis of Siewert type I adenocarcinoma of oesophagogastric junction – retain this evidence on the patient's medical records; do not submit a copy of this evidence in this authority application
Treatment criteria:
Patient must be undergoing treatment with this drug for the first time
AND
Patient must be undergoing treatment with this drug for metastatic disease (Stage IV disease) that is untreated with drug therapy; or
Patient must be undergoing treatment with this drug for locally advanced disease (Stage III disease) that is *either (i)* untreated with drug therapy, *(ii) treated with systemic therapy in the neoadjuvant/adjuvant setting, but the cancer has recurred after more than 6 months from the last dose of systemic therapy.*
AND
Treatment criteria:
Patient must be undergoing concomitant treatment with chemotherapy, at least at treatment initiation with this drug, containing a minimum of: (i) a platinum agent, plus (ii) a fluoropyrimidine agent
AND
Patient must have WHO performance status no higher than 1 at treatment initiation with this drug
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.
Restriction Type: ☒ Authority Required (STREAMLINED)
Indication: Advanced (Stage III) or metastatic (Stage IV) carcinoma of the following types: (i) Siewert type I adenocarcinoma of oesophagogastric junction, (ii) adenocarcinoma of oesophagus, (iii) squamous cell carcinoma of oesophagus
Treatment Phase: Continuing treatment
Clinical criteria:
The condition must not have progressed
AND
Treatment criteria:
Patient must be undergoing continuing treatment with this drug, with PBS-subsidised treatment having commenced through one of: (i) the 'Initial treatment' phase listing, (ii) 'Grandfather arrangements' listing; do not commence PBS-subsidised treatment through this treatment phase
AND
Treatment criteria:
Patient must not be undergoing continuing treatment through the PBS such that the total duration of treatment (as measured from the first dose of this drug, regardless if it was PBS-subsidised/non-PBS subsidised) goes beyond whichever comes first out of the following: (i) 24 months, (ii) 35 doses (based on a 3-weekly dose regimen), (iii) disease progression
Restriction Type: ☒ Authority Required (Streamlined)
Indication: Advanced (Stage III) or metastatic (Stage IV) carcinoma of the following types: (i) Siewert type I adenocarcinoma of oesophagogastric junction, (ii) adenocarcinoma of oesophagus, (iii) squamous cell carcinoma of oesophagus
Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements
Clinical criteria:
Patient must be currently receiving treatment with this drug for this PBS indication, with treatment having commenced prior to [PBS listing date]
AND
Clinical criteria:
Patient must have met all other PBS eligibility criteria that a non-'Grandfather' patient would ordinarily be required to meet, meaning that at the time non-PBS supply was commenced, the patient: (i) had a WHO performance status no greater than 1, (ii) was unsuitable for *either* surgical resection *or* chemoradiation, (iii) for a diagnosis of Siewert type I adenocarcinoma of oesophagogastric junction, there was evidence confirming HER2 negativity via immunohistochemistry in tumour material, (iv) was untreated with this drug, (v) for metastatic disease (Stage IV disease), the metastatic disease had yet to be treated with drug therapy, (vi) for locally advanced disease (Stage III disease), the locally advanced disease had yet to be treated with drug therapy *or disease recurrence must not have occurred within 6 months of completion of systemic therapy in the neoadjuvant/adjuvant setting*, (vii) was treated concomitantly with chemotherapy containing at least each of a platinum agent plus a fluoropyrimidine agent
AND
Clinical criteria:
The condition must not have progressed
Treatment criteria:
Patient must not be undergoing continuing treatment through the PBS such that the total duration of treatment (as measured from the first dose of this drug, regardless if it was PBS-subsidised/non-PBS subsidised) goes beyond whichever comes first out of the following: (i) 24 months, (ii) 35 doses (based on a 3-weekly dose regimen), (iii) disease progression
Administrative advice:

Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

For more detail on PBAC's view, see section 11 PBAC outcome.

10 Consideration of the evidence

10.1 A summary of how the resubmission addressed the outstanding issues is provided in the table below.

Table 15: Summary of changes made by the resubmission to address matters raised in the November 2021 PBAC PSD

Parameter	Resubmission changes	Comparison with November 2021 PBAC PSD
Effective ex-manufacturer price per 100 mg vial	$[redacted]	Compared to $[redacted] in submission and $[redacted] in PSCR. [redacted]% price reduction on PSCR price.
Restriction criteria	Proposed listing for advanced or metastatic (i) *[HER2 negative]* Siewert type I adenocarcinoma of GOJC, (ii) OAC, (iii) OSCC	Not consistent with paragraph 7.5. The resubmission did not propose an aligned restriction across all gastric, GOJ, and oesophageal cancers. Consistent with previous submission.
Economic evaluation		
Time horizon	7.5 years	Consistent with paragraph 7.15
Terminal care costs	Modified to capture the small difference in terminal care costs generated by discounting alone.	Not consistent with paragraph 7.15. Removing terminal care costs increased the ICER to $[redacted][1]/ QALY.
Extrapolation function	Gompertz (OS and PFS)	Consistent with paragraph 7.15.
ICER	$[redacted][1] per QALY	Consistent with paragraph 7.15
Financial estimates		
Patient estimates	Adjusted the proportion of GC patients who are GOJ from 50% to 34%. Included a small number of additional prevalent patients.	Consistent with paragraph 7.13. However, the resubmission did not provide financial estimates across all GOJ, gastric and oesophageal cancers.
Grandfathered patients	[redacted][2]	Unchanged from previous submission
RSA	Proposed a rebate of [redacted]% on expenditure above the cap.	Consistent with paragraph 7.15

PSD = Public Summary Document; PSCR = Pre-Sub-Committee Response; GOJ= gastro-oesophageal junction; ICER = incremental cost effectiveness ratio; OAC = oesophageal adenocarcinoma; OS = overall survival; OSCC = oesophageal squamous cell carcinoma; QALY = quality adjusted life years; RSA = risk sharing arrangement

The redacted values correspond to the following ranges:

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

[2] *< 500*

10.2 The table below outlines the financial implications estimated in the resubmission.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients treated						
Total patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net cost to MBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to PBS/RPBS/ MBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Previous submission (as provided in pre-PBAC response)						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Net cost to PBS/RPBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]

Source: Table 14 and Section 4 workbook provided with resubmission.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *$20 million to < $30 million*

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

[4] *$30 million to < $40 million*

10.3 The resubmission reduced the proportion of patients with gastric cancer (GC) who have GOJ from 50% to 34% and included a small number of additional prevalent GOJ patients.

10.4 The total net cost to the PBS/ RPBS of listing pembrolizumab was estimated to be $100 million to < $200 million over the first six years of listing (compared to $200 million to < $300 million in the previous submission).

10.5 The resubmission stated the sponsor is willing to enter into a risk sharing arrangement (RSA) with the Commonwealth on sharing the costs of the Commonwealth subsidy for supply of pembrolizumab for the first line treatment of patients with unresectable locally advanced or metastatic oesophageal carcinoma or HER2-negative Siewert Type 1 adenocarcinoma of the GOJ, in order to manage any risk to the overall cost to the PBS. The resubmission proposed a [redacted]% rebate on expenditure above the cap.

10.6 The resubmission noted PBAC's preference for "an aligned restriction across all gastric, GOJ and oesophageal cancers" which would be reflected in a combined cap across populations. The sponsor is willing to work with the PBAC and the Commonwealth to explore this possibility; however, raised a number of issues that would need to be resolved, including the need for transparency in agreeing patient numbers and adequately accounting for the different indications.

11 PBAC Outcome

11.1 The PBAC deferred making a recommendation to list pembrolizumab in combination with chemotherapy for the first line treatment of advanced or metastatic gastro-oesophageal cancers as defined by the specific tumour types included in the approved TGA indications. The PBAC advised further discussions were required regarding appropriate restriction criteria, a cost-effective price and parameters for a risk sharing arrangement.

11.2 The PBAC considered pembrolizumab's cost-effectiveness (as a first line treatment) would be acceptable at the same or lower cost per 3 weekly treatment cycle as for nivolumab (as a first line treatment) for gastro-oesophageal cancers.

11.3 The PBAC noted the restriction criteria proposed in the resubmission did not address the Committee's preference for an aligned restriction for patients with gastric, gastro-oesophageal junction and oesophageal cancers. The PBAC considered that, given the significant overlap in the anatomical distribution of these cancers, it would be appropriate for pembrolizumab (and nivolumab, should it be recommended) to be available for the first line treatment of advanced or metastatic 'gastro-oesophageal cancers' as defined by the specific tumour types included in the approved TGA Product Information document. The PBAC noted that, of the gastro-oesophageal cancers, pembrolizumab is currently approved by the TGA for the first line treatment of advanced or metastatic Siewert Type 1 adenocarcinoma of the GOJ, OAC and OSCC.

11.4 The PBAC noted an early resolution resubmission for nivolumab is concurrently being considered. The PBAC noted that, of the gastro-oesophageal cancers, nivolumab is currently approved by the TGA for the first line treatment of advanced or metastatic GOJ, GC and OAC and for the second line treatment of OSCC.

11.5 The PBAC reiterated its view that, although the indications are not fully aligned, there was likely to be significant overlap in patients that are treated with pembrolizumab or nivolumab in clinical practice. The PBAC considered a single listing for gastro-oesophageal cancers that allows treatment choice according to the TGA approved specific tumour types for each medicine was appropriate.

11.6 The PBAC noted there were differences in design and patient populations across the pembrolizumab and nivolumab trials, but considered that, overall, there was unlikely to be any difference between pembrolizumab and nivolumab in clinical practice for the first line treatment of gastro-oesophageal cancers in terms of clinical benefit, tolerability and treatment duration.

11.7 The PBAC noted with the exception of the terminal care costs, the revisions to the economic model were consistent with the November 2021 PSD. The PBAC noted the approach to costing terminal care was revised and as a result the ICER was appropriately not sensitive to this cost.

11.8 The PBAC considered an RSA would be required to appropriately manage the risk of use outside the proposed patient population. The PBAC considered the patient numbers included in the resubmission for the specific tumour types were reasonable but considered expenditure caps for gastro-oesophageal cancer covering all tumour types would need to be finalised with the Department.

Outcome:
Deferred

Addendum to the November 2021 PBAC PSD:

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

12 Background

12.1 The sponsor provided additional information in relation to the deferral of the decision to recommend listing of pembrolizumab on the PBS for gastro-oesophageal cancers (refer to paragraph **Error! Reference source not found.**).

12.2 Between its November 2021 and March 2022 meeting, the PBAC recommended the listing of nivolumab in combination with chemotherapy for the first line treatment of advanced or metastatic gastro-oesophageal cancers as defined by the specific tumour types included in the approved TGA indications.

12.3 At its March 2022 meeting, the PBAC recommended nivolumab for the second-line treatment of advanced or metastatic oesophageal squamous cell carcinoma who have failed one fluoropyrimidine and platinum-based chemotherapy treatment regimen and considered it would be cost-effective at the same price recommended for the first line treatment of gastro-oesophageal cancers. The PBAC considered it would be appropriate to implement a single listing for gastro-oesophageal cancers including the first and second line populations.

12.4 Pembrolizumab is currently approved by the TGA for the first line treatment of advanced or metastatic carcinoma of the oesophagus and HER2 negative gastroesophageal junction adenocarcinoma (tumour centre 1 to 5 centimetres above the gastroesophageal junction) that is not amenable to surgical resection or definitive chemoradiation. Nivolumab is currently approved by the TGA for the first line treatment of patients with HER2 negative advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma and for the second line treatment of patients with unresectable, advanced, recurrent or metastatic oesophageal squamous cell carcinoma.

13 Consideration of the evidence

Restriction criteria

13.1 The PBAC previously considered it would be appropriate for pembrolizumab to be available for the first line treatment of advanced or metastatic 'gastro-oesophageal

cancers' as defined by the specific tumour types included in the approved TGA Product Information document (paragraph **Error! Reference source not found.**). The additional information provided by the sponsor stated a listing that allows treatment choice according to the TGA approved specific tumour types is appropriate and supported.

13.2 The Secretariat proposed the following restriction wording.

MEDICINAL PRODUCT Form	PBS item code	Maximum amount	No. of Repeats
PEMBROLIZUMAB Injection	New (Public) New (Private)	200 mg	6
Available brands			
Keytruda (pembrolizumab 100 mg injection, 1 vial)			

	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required – Streamlined
	Episodicity: [blank]
	Severity: Advanced or metastatic
	Condition: gastro-oesophageal cancers
	Indication: Advanced or metastatic gastro-oesophageal cancers
	Treatment Phase: [blank]
	Clinical criteria:
	The condition must be a gastro-oesophageal cancer type as specified in the drug's 'Indications' section of the approved Australian Product Information
	AND
	Clinical criteria:
	The condition must be metastatic disease (Stage IV disease) that is untreated with drug therapy at treatment initiation with this drug; or
	The condition must be, at treatment initiation with this drug, locally advanced disease (Stage III disease) that is either: (i) untreated with drug therapy, (ii) treated with systemic neoadjuvant/adjuvant therapy, but the cancer has recurred after more than 6 months from the last dose of systemic therapy.
	AND
	Clinical criteria:
	Patient must be undergoing concomitant treatment with chemotherapy, at least at treatment initiation with this drug, containing a minimum of: (i) a platinum agent, plus (ii) a fluoropyrimidine agent
	AND
	Clinical criteria:
	Patient must have/have had, at the time of initiating treatment with this drug, a WHO performance status no higher than 1
	AND
	Clinical criteria:
	The condition must be unsuitable for each of: (i) surgical resection, (ii) chemoradiation
	AND
	Treatment criteria:
	Patient must not be undergoing treatment with this drug as a PBS-benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 months; annotate any remaining repeat prescriptions with the words 'cancelled' where this occurs
	CAUTION: In the first few months after starting immunotherapy, a transient tumour flare may occur that may be mistaken as disease progression despite an overall positive response to treatment.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.

	Administrative Advice: Special Pricing Arrangements apply.

13.3 The pre-PBAC response proposed a change to the clinical criteria 'The condition must be unsuitable for each of: (i) surgical resection, (ii) chemoradiation' to 'The condition must be unsuitable for either: (i) surgical resection or (ii) chemoradiation'.

13.4 The pre-PBAC response noted that, because the proposed restriction criteria does not specify HER2 status, the patient numbers for the financial estimates should reflect all patients, not just HER2 negative patients.

Cost effectiveness

13.5 The PBAC previously considered the cost-effectiveness of pembrolizumab (as a first line treatment) would be acceptable at the same or lower cost per 3 weekly treatment cycle as for nivolumab (as a first line treatment) for gastro-oesophageal cancers (paragraph **Error! Reference source not found.**).

13.6 The cost per 3 weekly treatment cycle for pembrolizumab and nivolumab (based on the published prices) is summarised in Table 2.

Table 2: Pembrolizumab and nivolumab cost per 3 weekly treatment cycle

	Pembrolizumab	Nivolumab
Dose per 3 weekly treatment cycle	200 mg	360 mg
Cost per 100 mg (published AEMP)	$3,823.75	$1,972.91
Cost per 3 weekly treatment cycle[1]	$7,647.50	$7,102.48

AEMP approved ex-manufacturer price;

1. Calculated as AEMP/ 100 mg x 3 weekly dose

Estimated patient numbers

13.7 The additional information provided by the sponsor stated that whilst the indications across the pivotal clinical studies for pembrolizumab and nivolumab (KN 590 and CM 649, respectively) are not fully aligned, there is an overlap in patients with Siewert Type I gastro-oesophageal junction cancer (GOJ) (Table 3). While the number of OC and Siewert Type 1 patients is consistent with previous PBAC consideration (500 to < 5,000 patients in Year 1, see Table 16), the number of Siewert Type II-III and gastric cancer patients provided was not evaluated. The pre-PBAC response acknowledged there is also an overlap in patients with oesophageal adenocarcinoma cancer (OAC), which accounts for approximately < 500 of the 500 to < 5,000 OC patients. The pre-PBAC response stated that, as the proposed restriction criteria included all patients with gastric cancer regardless of HER2 status, the estimated number of patients should be increased from 500 to < 5,000 to 500 to < 5,000.

Table 3: Total patients eligible for pembrolizumab or nivolumab in Year 1 (excluding grandfather patients)*

Year 1 - 2022	Oesophageal cancer	Gastro-oesophageal junction cancer		Gastric cancer
		Siewert Type I	Siewert Type II-III	
Pembrolizumab	~[redacted][1] patients	~[redacted][2] patients		
Nivolumab		~[redacted][2] patients	~[redacted][1] Patients	

Source: Table 1, additional information provided by sponsor
* The financial estimates previously included < 500 grandfathered patients
The redacted values correspond to the following ranges:
[1]500 to < 5,000
[2]< 500

13.8 A summary of the estimated number of patients expected to be treated with nivolumab for gastro-oesophageal cancers as defined by its approved TGA indications (see paragraph 12.4) is provided in Table 4.

Committee in Confidence

Table 4 : Estimated number of patients expected to be treated with nivolumab

[redacted]

[redacted]

End Committee in Confidence

Risk sharing arrangement

13.9 The sponsor emphasised the importance of alignment between the development of any expenditure caps associated with a risk sharing arrangement and the proposed restriction wording.

13.10 The sponsor stated that it would be unfair for a sponsor to be liable for any rebate that was being driven by an indication for which their drug was not approved at this time.

13.11 The sponsor stated it would be willing to consider a [redacted]% rebate of the treatment costs, should use exceed the expected use of pembrolizumab in that year.

For more detail on PBAC's view, see section 14 PBAC outcome.

14 PBAC outcome

14.1 The PBAC recommended the listing of pembrolizumab in combination with chemotherapy for the first line treatment of advanced or metastatic gastro-oesophageal cancers as defined by the specific tumour types included in the approved TGA indications. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of pembrolizumab (as a first line treatment) would be acceptable at the same or lower cost per 3 weekly treatment cycle as for nivolumab (as a first line treatment) for gastro-oesophageal cancers (paragraph 11.2). The PBAC considered it was appropriate for pembrolizumab to be included in the risk share arrangement recommended for nivolumab, with the expenditure caps increased to account for the expected additional use in the first line treatment of OSCC.

14.2 The PBAC recalled that nivolumab had been recommended for the treatment of advanced or metastatic gastro-oesophageal cancers as defined by the specific tumour types included in the approved TGA indications (paragraphs 12.2 and 12.3). The PBAC noted that the additional TGA indication approved for pembrolizumab is the first line treatment of OSCC, with nivolumab only approved for the second line treatment of OSCC. The PBAC considered the clinical need for effective treatments remained but if nivolumab is listed in line with PBAC's recommendation, would be limited to the first line treatment of patients with OSCC.

14.3 The PBAC noted the sponsor was supportive of a restriction criteria that limited access to the specific gastro-oesophageal cancer types included in the approved TGA indication. The PBAC advised the proposed restriction criteria in paragraph 13.2 was

appropriate with the following amendments (to ensure consistency with the criteria recommended for nivolumab at the March 2022 PBAC meeting):

- remove clinical criteria 'The condition must be unsuitable for each of: (i) surgical resection, (ii) chemoradiation' as 'not amenable to surgical resection or definitive chemoradiation' is specified as part of the TGA indications
- remove clinical criteria: 'The condition must be metastatic disease (Stage IV disease) that is untreated with drug therapy at treatment initiation with this drug'; or 'The condition must be, at treatment initiation with this drug, locally advanced disease (Stage III disease) that is either: (i) untreated with drug therapy, (ii) treated with systemic neoadjuvant/adjuvant therapy, but the cancer has recurred after more than 6 months from the last dose of systemic therapy'.
- remove clinical criteria: 'Patient must be undergoing concomitant treatment with chemotherapy, at least at treatment initiation with this drug, containing a minimum of: (i) a platinum agent, plus (ii) a fluoropyrimidine agent'.
- add clinical criteria: The treatment must be prescribed in accordance with the drug's 'Indications' section of the approved Australian Production Information with respect to each of: (i) concomitant drugs/therapies, (ii) line of therapy (i.e. prior drug treatments).
- amend treatment criteria: 'Patient must not be undergoing treatment with this drug as a PBS-benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 cumulative months from the first administered dose; annotate any remaining repeat prescriptions with the words 'cancelled' where this occurs' to 'Patient must not be undergoing treatment with this drug as a PBS-benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 months; annotate any remaining repeat prescriptions with the words 'cancelled' where this occurs'.
- add administrative advice: 'No increase in the maximum amount or number of units may be authorised.

14.4 The PBAC reiterated its previous consideration that while there were differences in design and patient populations across the pembrolizumab and nivolumab trials, overall, there was unlikely to be any difference between pembrolizumab and nivolumab in clinical practice for the first line treatment of gastro-oesophageal cancers in terms of clinical benefit, tolerability and treatment duration (paragraph 11.6). Additionally, the PBAC reiterated there was likely to be significant overlap in the patient populations in clinical practice due to overlap in anatomical distribution of these cancers and there was a risk pembrolizumab would be used in Siewert type II and III gastro-oesophageal junction cancer and gastric cancer (paragraph 3.6 and 5.3).

14.5 The PBAC recalled that the sponsor did not previously differentiate between patients with OAC, OSCC and GOJC when supporting the claim of cost effectiveness for pembrolizumab. Further, given the reasons outlined in paragraph 14.4, the PBAC considered there was no basis to conclude the cost effectiveness of first line treatments would be any different for OAC, OSCC and GOJC and it was reasonable to assume the immunotherapies would be of similar cost effectiveness across the specific tumour types. The PBAC considered that the cost effectiveness of pembrolizumab for the first line treatment of OSCC (at the price recommended in paragraph 14.1) was likely to be similar to the first line treatment of other gastro-oesophageal cancers.

14.6 The PBAC noted the additional patients accounted for by pembrolizumab compared to nivolumab were the OSCC patients eligible for first line treatment. The PBAC noted that, as acknowledged in the pre-PBAC response, of the 500 to < 5,000 patients eligible for first line treatment with pembrolizumab in Year 1, approximately < 500 would have OSCC. The PBAC considered this proportion (< 500/500 to < 5,000 = 30%) could be applied to the treated patients in Year 2 to 6 of listing (see Table) to estimate the number of OSCC patients eligible for first line treatment. The PBAC noted a number of these patients (as outlined in **Error! Reference source not found.**) would have been treated with nivolumab in the second line setting. The PBAC considered the net financial cost of listing pembrolizumab should account for the first line treatment of patients with OSCC not already accounted for in the second line setting. The PBAC noted patients in the first line setting would be treated for 32.9 weeks (calculated from Table 12) compared to 26.0 weeks in the second line setting (calculated from Table 15, nivolumab PSD, July 2021 PBAC meeting) and the net financial implications should account for this difference.

14.7 The PBAC noted that < 500 patients will require transitioning to PBS supply (see **Error! Reference source not found.**) and a separate restriction criteria is not required for these patients as they would meet the restriction criteria proposed in Section 15. The PBAC considered these patients would not be accounted for in the patient numbers in **Error! Reference source not found.** and it is appropriate for them to be added to the net financial estimates for pembrolizumab, accounting for a reduced treatment duration.

14.8 The PBAC considered the increase in Siewert type II and III gastro-oesophageal cancer and gastric cancer patient numbers proposed in the pre-PBAC response (paragraph 13.7) were not supported and recalled the number of patients recommended during its consideration of nivolumab was as defined by its approved TGA indications (see Table 19).

14.9 The PBAC noted the sponsor raised concerns in its pre-PBAC response regarding the appropriateness of sponsors being liable for rebates driven by an indication for which their drug was not TGA approved (paragraph 13.10). However, the PBAC noted the

challenges in distinguishing the specific tumour types in clinical practice and risk of use outside the TGA approved specific tumour types (paragraph 14.4) and considered that, overall, it would be reasonable for pembrolizumab to join the same RSA for gastro-oesophageal cancers recommended for nivolumab with the same parameters. The PBAC considered it was appropriate to adjust the expenditure caps to account for the revised financial estimates as outlined in paragraphs 14.6 and 14.7.

14.10 The PBAC advised that pembrolizumab is not suitable for prescribing by nurse practitioners as antineoplastic agents are currently out of scope for prescribing by nurse practitioners.

14.11 The PBAC recommended that the Early Supply Rule should not apply as it currently does not apply to Section 100 Efficient Funding of Chemotherapy listings.

14.12 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

14.13 The PBAC found that the criteria prescribed by the National Health (Pharmaceutical 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 nivolumab;

b) The treatment is not expected to address a high and urgent unmet clinical need as nivolumab has been recommended for all populations (noting OSCC patients can only access treatment in the second line setting); and

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.

Outcome:
Recommended

15 Recommended listing

15.1 Add indication on a separate PBS item code as follows:

MEDICINAL PRODUCT Form	PBS item code	Maximum amount	No. of Repeats
PEMBROLIZUMAB Injection	New (Public) New (Private)	200 mg	6
Available brands			
Keytruda (pembrolizumab 100 mg injection, 1 vial)			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒ Medical Practitioners			
Restriction type: ☒ Authority Required (STREAMLINED)			
Episodicity: [blank]			
Severity: Advanced or metastatic			
Condition: gastro-oesophageal cancers			
Indication: Advanced or metastatic gastro-oesophageal cancers			
Treatment Phase: [blank]			
Clinical criteria:			
The condition must be a gastro-oesophageal cancer type as specified in the drug's 'Indications' section of the approved Australian Product Information			
AND			
Clinical criteria:			
The treatment must be prescribed in accordance with the drug's 'Indications' section of the approved Australian Production Information with respect to each of: (i) concomitant drugs/therapies, (ii) line of therapy (i.e. prior treatments, if any)			
AND			
Clinical criteria:			
Patient must have/have had, at the time of initiating treatment with this drug, a WHO performance status no higher than 1			
AND			
Treatment criteria:			
Patient must not be undergoing treatment with this drug as a PBS-benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 cumulative months from the first administered dose; annotate any remaining repeat prescriptions with the words 'cancelled' where this occurs			
CAUTION: In the first few months after starting immunotherapy, a transient tumour flare may occur that may be mistaken as disease progression despite an overall positive response to treatment.			
Administrative advice: No increase in the maximum 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.			

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

16 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.

17 Sponsor's Comment

MSD welcomes the positive recommendation made by the PBAC for Keytruda in the first-line treatment of gastro-oesophageal cancers. With no recently funded novel systemic treatment for first-line oesophageal squamous cell carcinoma, MSD is pleased that all Australian oesophageal cancer patients will soon have access to Keytruda.

MSD will work closely with the Department of Health to ensure the broad listing proposed by the PBAC is adequately accounted for in any associated RSA so that Keytruda is made available to eligible Australian patients as soon as possible.