7.07 PEMBROLIZUMAB, Powder for injection 50 mg, Solution concentrate for I.V. infusion 100 mg in 4 mL, Keytruda®, Merck Sharp & Dohme (Australia) Pty Ltd

1 Purpose of submission

1.1 The resubmission requested a Section 100 (Efficient Funding of Chemotherapy) (S100 EFC) Authority Required listing of pembrolizumab for the first-line treatment of patients with metastatic (Stage IV) non-small cell lung cancer (NSCLC), whose tumours do not have an activating epidermal growth factor receptor (*EGFR*) gene mutation or an anaplastic lymphoma kinase (*ALK*) gene rearrangement in tumour material, and whose tumours express high levels of programmed cell death ligand 1 (PD-L1), defined as a tumour proportion score (TPS) of ≥50%.

1.2 The integrated codependent resubmission also requested the Medical Services Advisory Committee (MSAC) reconsider a Medical Benefits Schedule (MBS) listing of immunohistochemistry (IHC) testing for the evaluation of PD-L1 expression to determine if the requirements relating to PD-L1 status for PBS eligibility to pembrolizumab are met.

Table 1: Evidence provided in the submission to support the use of the codependent technology

Component	Description
Population	Test: Patient diagnosed with NSCLC Medicine: Stage IV NSCLC in patients with performance status of 0 or 1 whose tumours are *EGFR* wildtype and *ALK* translocation negative[a] and express high level of PD-L1 (defined as TPS of ≥50%).
Intervention	Test: PD-L1 IHC testing Medicine: Pembrolizumab 200 mg IV every 3 weeks
Comparator	Test: No testing Medicine: Platinum-based doublet chemotherapy
Outcomes	OS, PFS and safety
Clinical claim	In Stage IV NSCLC patients with performance status of 0 or 1 whose tumours express PD-L1 (≥50%) and are *EGFR* wildtype and *ALK* translocation negative, pembrolizumab is more effective than platinum-based doublet chemotherapy at improving PFS, OS and safety

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; IHC = Immunohistochemistry; IV = intravenous; NSCLC = non-small cell lung cancer; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; TPS = tumour proportion score

[a] *EGFR* test and *ALK* test are conducted only in patients with non-squamous or not otherwise specified NSCLC. Squamous NSCLCs are considered as *EGFR* wildtype and *ALK* negative

Source: Revised from Table 1.1-3, p18 of the resubmission

2 Requested listings

2.1 The requested PBS listings are shown below. The resubmission requested a Special Pricing Arrangement (SPA).

Proposed PBS Listing

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
PEMBROLIZUMAB 50 mg injection: powder for, 1 vial [a] 100 mg/4 mL injection, 1 vial [a]	200 mg	5 (initial)[a] 7 (continuing)	Published price: $9,023.83 (public)[b] $9,187.35 (private)[b] Effective price[c]: $[redacted] (public)[b] $[redacted] (private)[b]	Keytruda® Merck Sharp & Dohme (AU) Pty Ltd

Treatment phase: Initial treatment

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Stage IV (metastatic) previously untreated
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) previously untreated non-small cell lung cancer
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	The condition must be previously untreated, **AND** The treatment must be the sole PBS-subsidised therapy for this condition, **AND** Patient must have a WHO performance status score of 0 or 1, **AND** The treatment must not exceed a total of 6 doses at a maximum dose of 200 mg every 3 weeks.
Population criteria:	Patient must have evidence of at least 50% programmed cell death ligand 1 (PD-L1) in tumour material, **AND** Patient must have no evidence of an activating epidermal growth factor receptor (EGFR) gene or of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.
Administrative Advice	No increase in the maximum number of repeats will be authorised. 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. Special pricing arrangements apply.

[a] Both for initial treatment and continuing treatment
[b] The dispensed prices have been recalculated using the Efficient Funding of Chemotherapy (EFC) fees as updated in July 2017.
[c] Prices related to proposed special price arrangement

Treatment phase: Grandfathering

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Stage IV (metastatic) previously untreated
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) previously untreated non-small cell lung cancer
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition, **AND** Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to (date of listing), **AND** Patient must have a WHO performance status of 0 or 1, **AND** The treatment must not exceed a total of 6 doses at a maximum dose of 200 mg every 3 weeks.
Population criteria:	Patient must have evidence of at least 50% programmed cell death ligand 1 (PD-L1) in tumour material, **AND** Patient must have no evidence of an activating epidermal growth factor gene or of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.
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. Special Pricing Arrangements apply.

Treatment phase: Continuing treatment

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Stage IV previously untreated
Condition:	Non-small cell lung cancer
PBS Indication:	Stage IV (metastatic) previously untreated non-small cell lung cancer
Treatment phase:	Continuing
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must not have progressive disease, **AND** Patient must have previously been issued with an authority prescription for this drug for this indication, **AND** The treatment must not exceed a dose of 200 mg every 3 weeks, **AND** Treatment must not exceed 35 administrations or 2 years of continuous treatment.
Administrative Advice	No increase in the maximum number of repeats will be authorised. Special pricing arrangements apply

2.2 The requested PBS patient population in the resubmission is consistent with the population proposed in the pre-PBAC response to the March 2017 PBAC meeting. These changes have been maintained in this resubmission and are outlined below:

- the disease stage is limited to Stage IV (vs Stage IIIB/IV in the previous submission);
- patients should have a performance status of 0 or 1 to be eligible for pembrolizumab (vs any performance status in the original submission); and
- retreatment of patients who have progressive disease after achieving an initial objective response to pembrolizumab has been removed from the PBS restriction.

2.3 These revisions are consistent with the trial protocol in KN-024 and the TGA-approved product information (PI). The PBAC considered that these changes to the proposed restriction were appropriate.

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

3 Background

Registration Status

3.1 In March 2017, pembrolizumab was approved by the TGA for the treatment of previously untreated metastatic NSCLC patients with tumours that are PD-L1 TPS ≥50% (as determined by a validated test), *EGFR* wildtype and *ALK* translocation negative.

3.2 Other TGA-approved indications include:

- Advanced NSCLC whose tumours express PD-L1 with a ≥1% TPS (as determined by a validated test) and who have received platinum-containing chemotherapy.
- Unresectable or metastatic melanoma in adults, as monotherapy.
- Recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy.

Previous PBAC consideration

3.3 This is the second integrated codependent technology submission to the PBAC and MSAC for pembrolizumab for (i) the first-line treatment of NSCLC in patients whose tumour expresses express PD-L1 at TPS ≥50% and (ii) PD-L1 testing. The first integrated codependent submission was considered by both committees in March and April 2017 respectively.

3.4 Pembrolizumab is currently listed on the PBS for unresectable Stage III or Stage IV malignant melanoma, regardless of PD-L1 expression.

3.5 At the March 2017 PBAC meeting, an integrated codependent submission to list pembrolizumab as first-line treatment for patients with Stage IIIB/IV, PD-L1 TPS ≥50% NSCLC was rejected by the PBAC on the basis of unfavourable and uncertain cost-effectiveness. The PBAC also advised that there was uncertainty in selecting a PD-L1 expression threshold to define an optimal patient population mostly likely to respond to treatment (Item 6.04, public summary document (PSD), March 2017).

3.6 At the April 2017 MSAC meeting, Application No. 1440 – PD-L1 testing for access to pembrolizumab for first-line treatment of locally advanced or metastatic NSCLC was considered. MSAC did not support public funding of PD-L1 IHC as a companion diagnostic test for selecting patients with NSCLC for treatment with pembrolizumab. MSAC considered that PD-L1 IHC as a companion diagnostic test has insufficient evidence of analytical validity (and documented poor reproducibility), weak evidence of clinical validity (lacks ability to predict response to therapy) and weak evidence of clinical utility (insufficient information to guide treatment) (Application No. 1440, PSD, April 2017 MSAC meeting).

4 Population and disease

4.1 Lung cancer is the fifth most commonly diagnosed invasive cancer and is the leading cause of cancer death in Australia. All patients suspected of having NSCLC undergo a biopsy at initial diagnosis to determine histology. For patients with NSCLC of

squamous histology, assessment of PD-L1 status through IHC will be the only biomarker test undertaken at diagnosis. For patients who have non-squamous or not otherwise specified NSCLC, PD-L1 IHC testing will be performed at initial diagnosis, along with *EGFR* and *ALK* testing.

4.2 The submission proposed that a patient with Stage IV NSCLC whose tumour has ≥50% PD-L1 expressing cells, is *EGFR* wild-type and *ALK* translocation negative[1], and has a performance status of 0 or 1, be eligible for first-line treatment with pembrolizumab. A patient diagnosed with earlier stage disease and tested for PD-L1 at that time would only become eligible for pembrolizumab after progressing to Stage IV (and the other requirements are met). However, given the evidence that PD-L1 expression varies during the disease course, re-biopsy on disease progression to Stage IV disease would be required to ensure patients receive the correct treatment.

5 Comparator/s

5.1 The re-submission nominated current practice, i.e. no test and treatment with platinum-based doublet chemotherapy for all patients, as the main comparator. This is unchanged from the previous submission and was accepted by the MSAC and PBAC.

5.2 The PBAC considered that pembrolizumab would displace, not replace, use of platinum-based doublet chemotherapies in the proposed target population.

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 seven individuals via the Consumer Comments facility on the PBS website. The comment supported the PBS listing of pembrolizumab for NSCLC and other rare cancers.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the submission, on the basis of increased survival benefit and decreased toxicity. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) in this context as being 5 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[2],

[1] Patients with squamous NSCLC do not undergo EGFR test and ALK testing but are considered EGFR wild-type and ALK translocation negative.

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

based the KN-024 comparison of pembrolizumab with platinum-based doublet chemotherapy.

Overview of the evidence base

6.4 The resubmission presented evidence that has been linked to support the claim that targeting treatment-naïve patients with PD-L1 TPS ≥50% NSCLC with pembrolizumab will improve progression-free survival (PFS), overall survival (OS) and safety compared with platinum-based doublet chemotherapy (Table 2). The same approach was used in the previous submission.

Table 2: Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in clinical trials
Accuracy and performance of the test (analytical validity)	A study of test accuracy with the evidentiary standard using the ≥50% TPS threshold	☒ k=5 n=700	k=3 low risk of bias k=2 unclear risk of bias
Prognostic evidence	Comparison of outcomes in patients receiving usual care conditioned on the presence or absence of the biomarker	☒ k=8 n=12,939	Low risk of bias
Change in patient management	Evidence to show that biomarker determination guides decisions about treatment with the medicine	☐ k=0 n=0	
Treatment effectiveness			
Predictive effect	Comparison of outcomes in patients with or without the biomarker who receive the medicine or its comparator	☒ k=2 n=142	High risk of bias as it is an indirect comparison
Treatment effect (enriched)	Single randomised controlled trial of medicine vs current care in patients that are test positive in both arms	☒ k=1 n=305	PFS and OS: low risk of bias Safety, QoL: high risk of bias
Other	Single arm PD-L1 unselected chemotherapy trials versus KN-001 and KN-024	☒ k=8 n=2,129	High risk of bias as it is an indirect comparison

K = number of studies, n = number of patients
[a] reference standard available
[b] Reference standard not available
Source: Table constructed during the evaluation, based on Section 2 of the resubmission

Table 3: Data availability to inform comparisons

Proposed test vs no test	No studies	
Proposed test vs alternative test	Ratcliffe et al, 2017; Rimm et al, 2017; Adam et al, 2016; Scheel et al, 2016	
	Pembrolizumab	**Platinum-based doublet chemotherapy**
Biomarker test positive	KN-024, KN-001	KN-024
Biomarker test negative	KN-001	No studies
Biomarker unselected	No studies	Gronberg, 2009; Sandler, 2000; Scagliotti, 2008; Thomas, 2006; Yamamoto, 2006; Zatlouka, 2003

Source: Table constructed during the evaluation, based on Section 2 of the resubmission

6.5 The resubmission provided new concordance data from Rimm et al 2017 and Adam et al 2016, which compared the four commercially available tests and compared laboratory developed tests with the evidentiary standard, as well as new evidence from six studies enrolling biomarker-unselected patients who received platinum-based doublet chemotherapy. The other clinical studies have been considered by the PBAC at the March 2017 meeting and/or by the MSAC at the April 2017 meeting.

6.6 No evidence was presented on the effectiveness of the comparator in a biomarker negative population. The evidence provided for the effectiveness of pembrolizumab in a biomarker negative population is also limited to a few treatment naïve patients enrolled in a phase II trial (KN-001). Thus, a direct comparison of the effectiveness of both the proposed medicine and the current standard of care in the biomarker positive population compared to the biomarker negative population is not possible (predictive effect). The resubmission has provided data on the effectiveness of platinum-based doublet chemotherapy (comparator) in a biomarker unselected population as a surrogate for the biomarker negative population. Given that 22%-29% of the Australian NSCLC population have a tumour which is PD-L1 positive (TPS ≥50%), the use of this evidence as a surrogate is problematic.

6.7 There are differences in the populations enrolled in the KN-024 and KN-001 trials that may or may not affect clinical outcomes. The studies enrolling biomarker-unselected patients are a poor surrogate for biomarker negative studies and the baseline characteristics of the patients enrolled in these studies are highly variable. Thus, the indirect comparisons undertaken with these studies are subject to a high risk of bias.

Comparative effectiveness (based on direct evidence only)

6.8 No direct evidence was presented.

Comparative effectiveness (based on linked evidence)

6.9 Details of the treatment trials presented in the resubmission are provided in the table below. KN-024 was the key trial in the previous submission. No additional direct trial comparing pembrolizumab with platinum-based doublet chemotherapy in the proposed PBS population was identified by the resubmission.

Table 4: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
KN-024	Clinical study report KN-024 A randomized open-label Phase III trial of pembrolizumab versus (vs.) platinum based chemotherapy in first-line (1L) subjects with programmed cell death 1 ligand 1 (PD-L1) Strong Metastatic Non-Small Cell Lung Cancer (NSCLC). CSR Identification P024V01MK3475 Publication Reck, M, Rodriguez-Abreu, D, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer.	11 July 2016 New England Journal of Medicine 2016; 375(19):1823-33

Source: Table 2.2-4, pp73-74 of the resubmission.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Patient population	Outcome(s)	Use in modelled evaluation
Direct comparison of pembrolizumab and platinum-based doublet chemotherapy in PD-L1 positive ≥50% NSCLC					
KN-024	305	R (1:1), OL, MC • Pembrolizumab 200 mg Q3W • Platinum-based doublet chemotherapy Stratification: by ECOG (0 vs 1), region (east Asia vs non East Asia) and histology (squamous vs non-squamous). Retreatment with pembrolizumab was allowed in the protocol[a] Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Switching was allowed from chemotherapy to pembrolizumab[b]	Treatment naïve PD-L1 highly positive (TPS ≥50%) Stage IV NSCLC with no evidence of *EGFR* mutation or *ALK* translocation	Primary: PFS per RECIST 1.1 based on BICR review Secondary: OS, ORR, QoL, safety	Used

ALK = anaplastic lymphoma kinase; BICR = blinded independent central radiology; NSCLC =non-small cell lung cancer; ORR = objective response rate; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; MC = multi-centre; OL = open label; OS = overall survival; PFS = progression-free survival; QoL = Quality of life; Q3W = every three weeks; R (1:1) = randomised 1 to 1 ratio; TPS = tumour proportion score.

[a] The eligibility criteria for retreatment in KN-024 were: experienced disease progression after stopping initial treatment with pembrolizumab due to attaining a confirmed complete response (CR); treated for at least six months with pembrolizumab; and received at least two treatments with pembrolizumab beyond the date when the initial CR was declared; AND did not receive any anti-cancer treatment since the last dose of pembrolizumab; OR patients had stable disease (SD); partial response (PR) or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability (Section 7.1.5.5, p90 KN-024 Protocol).

Source: Table compiled during the evaluation from the submission and the KN-024 clinical study report.

6.10 The risk of bias and confounding in KN-024 differed for the different outcomes:

- There was a low risk of bias for PFS, as disease progression was determined by independent radiologists without knowledge of patient treatment assignment.
- Assessment of OS had a low risk of confounding. Patients randomised to the chemotherapy arm were allowed to receive second-line immunotherapy, i.e. pembrolizumab, upon progression. However, this treatment switching would reflect current clinical practice, as another PD-L1/PD-1 inhibitor (nivolumab)

has been listed on the PBS for treatment of patients with locally advanced or metastatic NSCLC who have progressed on or after prior platinum-based doublet chemotherapy, regardless of PD-L1 status (recommended at the March 2017 PBAC meeting).

- Assessment of subjective safety outcomes and other patient-reported quality of life (QoL) outcomes were likely to be biased given that patients and investigators were aware of treatment allocation.

6.11 The previous submission presented results of PFS and OS from KN-024, based on median follow-up of 11 months.

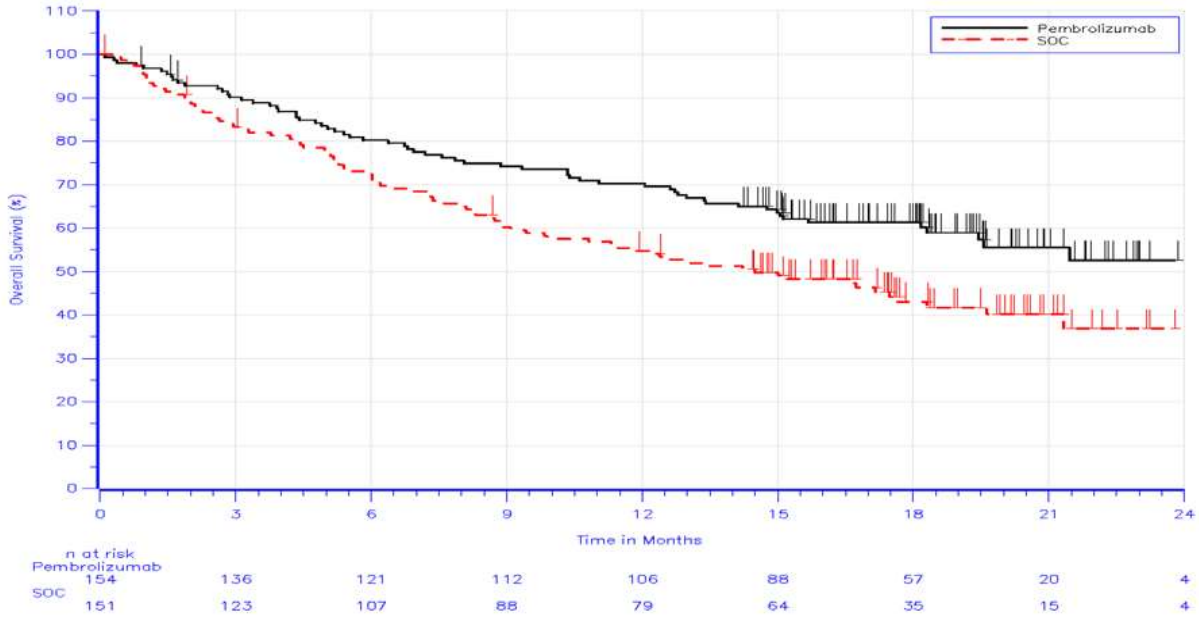
6.12 The updated OS results from KN-024 (median follow-up of 19 months) are presented in the table below. These data, although not presented in the previous submission, were provided in the pre-PBAC response and were considered by the PBAC at its March 2017 meeting.

Table 6: Updated results of OS (19 months median follow-up[a]), ITT population, KN-024

Treatment	Events n/N (%)	Person-months	OS rate at Month 12 (95% CI)	Median OS (months)[b] (95% CI)	HR[c] (95% CI) p-value[d]
Pembrolizumab	63/154 (40.9%)	[redacted]	70.3% [redacted]	Not reached (14.9, not reached)	0.63 (0.46, 0.88) p = 0.003
Chemotherapy	84/151 (55.6%)	[redacted]	54.8% [redacted]	14.5 (9.8, 19.6)	

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival
[a] Database cut-off date: 5 January 2017
[b] From product-limit (Kaplan-Meier) method for censored data.
[c] Pembrolizumab vs chemotherapy. Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs non-East Asia), performance status (0 vs 1) and histology (squamous vs non-squamous).
[d] One-sided p-value based on log-rank test.
Source: Table 2.5-2, p98 of the resubmission

Figure 1: Kaplan-Meier plot of OS (19 months median follow-up[a]), ITT population



ITT = intention-to-treat; OS = overall survival; SOC = standard of care
[a] Database cut-off date: 5 January 2017
Source: Figure 2.5-2, p99 of the resubmission

6.13 The updated results (based on median follow-up of 19 months) were similar to those presented in the original submission (HR: 0.60; 95% CI: 0.41, 0.89), and did not alter any of the previous conclusions regarding the comparative effectiveness of pembrolizumab versus chemotherapy in treatment-naïve patients with PD-L1 TPS ≥50% NSCLC.

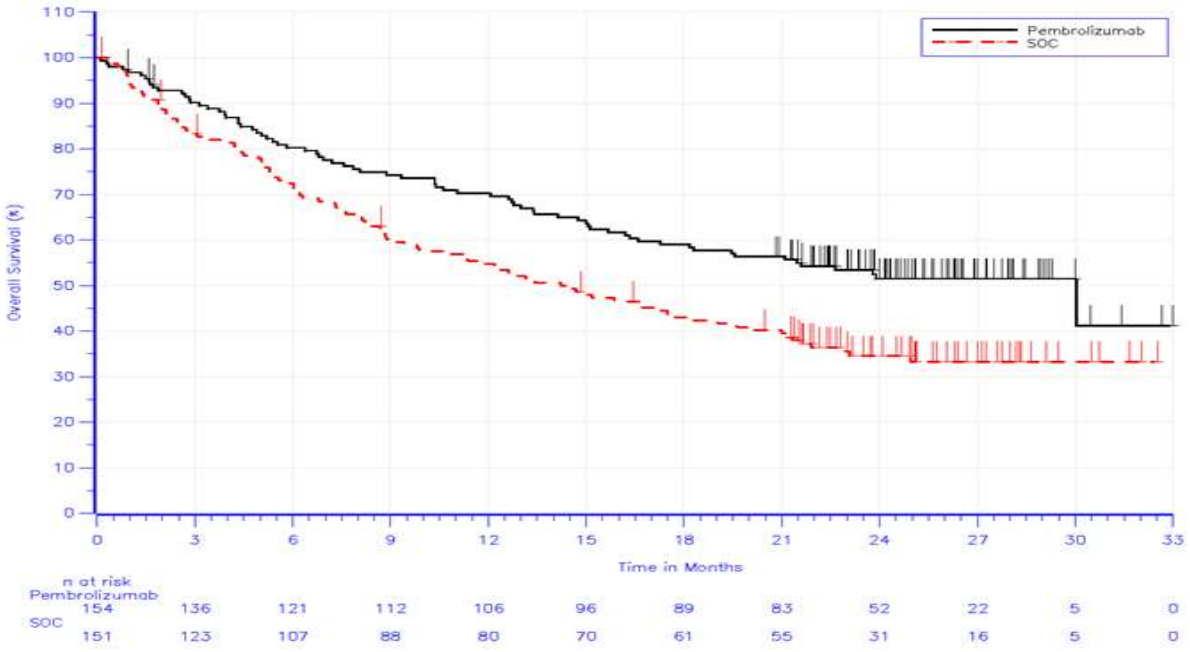
6.14 The PSCR (p1, 9, 10) provided updated results (final analysis of KN-024) for PFS and OS based on a median follow-up of 25 months. The updated OS results and Kaplan-Meier curves are presented below.

Table 7: Further updated results of OS from the final analysis of KN-024 (25 months median follow-up[a]), ITT population

Treatment	Events n/N (%)	OS rate at Month 12 (95% CI)	Median OS (months)[b] (95% CI)	HR[c] (95% CI) p-value[d]
Pembrolizumab	73/154 (47.4%)	70.3% [redacted]	30.0 (18.3, not reached)	0.63 (0.47, 0.86) p = 0.002
Chemotherapy	96/151 (63.6%)	54.8% [redacted]	14.2 (9.8, 19.0)	

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival
[a] Database cut-off date: 10 July 2017
[b] From product-limit (Kaplan-Meier) method for censored data.
[c] Pembrolizumab vs chemotherapy. Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs non-East Asia), performance status (0 vs 1) and histology (squamous vs non-squamous).
[d] One-sided p-value based on log-rank test.
Source: Table 1, p9 of the PSCR

Figure 2: Kaplan-Meier plot of OS (25 months median follow-up[a]), ITT population



ITT = intention-to-treat; OS = overall survival; SOC = standard of care
[a] Database cut-off date: 10 July 2017
Source: Figure 1, p10 of the PSCR

6.15 The PSCR (p1) stated that the OS benefit of pembrolizumab relative to platinum-based doublet chemotherapy was maintained in the final analysis of the KN-024 trial. The Economic Sub-committee of the PBAC and Evaluation Sub-committee of MSAC

(ESCs) noted that the updated data is consistent with the results presented in the resubmission, from 19 months median follow-up. However, the ESCs also noted that, although the median duration of follow-up had increased to 25 months, less than half of the patients in the pembrolizumab arm had died during the period of follow-up. The OS data, therefore, remained immature to reliably estimate the long-term survival benefits of pembrolizumab versus platinum-based doublet chemotherapy in the proposed target population.

6.16 The PSCR (p9) further provided survival outcomes for 1) PD-1/PD-L1 inhibitors in the second-line setting, 2) other targeted therapies for non-small cell lung cancer, and 3) pembrolizumab in melanoma patients, as "context" for the results from KN-024. The ESCs considered that a comparison of the OS results from KN-024 with the OS results for pembrolizumab or other targeted therapies for treatment of other indications could not help resolve the concern regarding the uncertainty surrounding the cost-effectiveness associated with the proposed listing of PD-L1 testing and pembrolizumab relative to the current standard of care, namely no testing + platinum-based doublet chemotherapy.

6.17 The pre-PBAC response (p1) argued that, for a setting where the historical median survival was approximately 12 months[3], the median survival of 30 months in the pembrolizumab arm of KN-024 represents a dramatic improvement in patient outcomes which reflects the durable efficacy of pembrolizumab. The pre-PBAC response stated that the consistency in OS results from different data-cuts (HR = 0.63 [95% CI 0.46, 0.88] at 19 months, vs HR = 0.63 [95% CI 0.47, 0.86] at 25 months) also provide confidence in clinical conclusions. The PBAC agreed with the pre-PBAC response that the evidence at 25 months was robust and confirmed earlier trial results, however the Committee considered that there was nonetheless uncertainty in the magnitude of long-term survival benefits of pembrolizumab over platinum-based doublet chemotherapy.

Comparative harms

6.18 No updated comparative data were provided by the resubmission regarding the safety of pembrolizumab versus platinum-based doublet chemotherapy for treatment of PD-L1 positive (TPS ≥50%) NSCLC patients.

6.19 After the end of the reporting period of the most recent Periodic Safety Updated Report (PSUR) (covering the period from 4 September 2016 to 3 March 2017) and during the preparation of the PSUR, the Marketing Authorisation Holder (MAH) determined that: 1) there is a possible causal association between encephalitis and pembrolizumab; and 2) sarcoidosis is considered an adverse drug reaction associated with pembrolizumab exposure. The MAH intends to update the Company Core Data Sheets and the pembrolizumab core Risk Management Plan to reflect these late-breaking changes.

[3] Noonan et al, 2015, The Influence of the Evolution of First-Line Chemotherapy on Steadily Improving Survival in Advanced Non-Small-Cell Lung Cancer Clinical Trials, Vol 10, Issue 11, Pages 1523-153

Benefits and harms

6.20 A summary of the comparative benefits and harms for pembrolizumab 200 mg every 3 weeks versus platinum-based doublet chemotherapy in first-line NSCLC patients whose tumours express a high level of PD-L1 (TPS ≥50%) is presented in the table below.

Table 8: Summary of comparative benefits and harms for pembrolizumab and chemotherapy in first-line NSCLC patients whose tumours express a high level of PD-L1 (TPS ≥50%)

Benefits					
	Pembrolizumab (N=154)	**Platinum-based doublet chemotherapy (N=151)**	**Absolute difference**	**HR (95% CI)**	
OS, median follow-up 25 months (further updated results)[a]					
Death, n (%)	73 (47.4%)	96 (63.6%)	-16.2%		
% surviving at Month 12 (95% CI)	70.3% [redacted]	54.8% [redacted]	15.5%		
OS median, months (95% CI)	30.0 (18.3, NR)	14.2 (9.8, 19.0)	15.8	0.63 (0.47, 0.86)	
OS, median follow-up 11 months[b]					
Death, n (%)	44 (28.6%)	64 (42.4%)	-13.8%		
% surviving at Month 12 (95% CI)	[redacted]	[redacted]	[redacted]		
OS median, months (95% CI)	NR (NR, NR)	NR (9.4, NR)	Not estimable	0.60 (0.41, 0.89)	
PFS, median follow-up 11 months[b]					
Disease progression or death, n (%)	73 (47.4%)	116 (76.8%)	-29.4%		
% progression-free surviving at Month 12 (95% CI)	[redacted]	[redacted]	[redacted]		
PFS median, months (95% CI)	10.3 (6.7, NR)	6.0 (4.2, 6.2)	4.3	0.50 (0.37, 0.68)	

Harms[c]						
	Pembrolizumab (N=154)	**Platinum-based doublet chemotherapy (N=151)**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				Pembrolizumab (N=154)	**Platinum-based doublet chemotherapy (N=151)**	
Treatment-related[d] AEs						
Any grade	113/154	135/150	0.82 (0.73, 0.91)	73.4	90.0	-16.6% (-25.1%, -8.1%)
Grade 3, 4 or 5	41/154	80/150	0.50 (0.37, 0.68)	26.6	53.3	-26.7% (-37.3%, -16.1%)
Immune-mediated AEs						
Any grade	45/154	7/150	6.26 (2.92, 13.44)	29.2	4.7	24.5% (16.6%, 32.5%)
Grade 3,4 or 5	15/154	1/150	14.61 (1.95, 109.23)	9.7	0.7	9.0% (4.2%, 13.9%)
○ Pneumonitis	4/154	1/150	3.90 (0.44, 34.46)	2.6	0.7	1.9% (-0.9%, 4.8%)

AE = adverse event; CI = confidence interval; HR = hazard ratio; NR = not reached; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; RD = risk difference; RR = relative risk

[a] Database cut-off date: July 2017; median duration of follow-up 25.2 months. OS data remain immature.

[b] Database cut-off date: May 9, 2016; median duration of follow up of 11.2 months (range 6.3 to 19.7 months).

[c] AEs were followed up for 30 days after last dose of study treatment.

[d] Events were attributed to treatment by the investigator and indicated by the investigator on case-report form.

Source: Compiled during the evaluation from effectiveness and safety data presented in the previous submission and this resubmission

6.21 On the basis of the evidence presented in the submission, for treatment naïve Stage IV NSCLC patients (with no evidence of *EGFR* activating mutation or *ALK*

translocation) with evidence of high tumour expression of PD-L1 (TPS ≥50%), treatment with pembrolizumab instead of first-line platinum-based doublet chemotherapy for a median duration of 25 months, the risk of death would be reduced by 37%. However, whilst there was a statistically significant overall survival benefit associated with pembrolizumab over chemotherapy, the data was immature overall.

6.22 On the basis of the evidence presented in the submission, for treatment naïve Stage IV NSCLC patients (with no evidence of *EGFR* activating mutation or *ALK* translocation) with evidence of high tumour expression of PD-L1 (TPS ≥50%), treatment with pembrolizumab instead of first-line platinum-based doublet chemotherapy for a median duration of 11 months, the risk of disease progression or death would be reduced by a statistically significant 50%.

6.23 For every 100 patients who are followed-up for 30 days after the last dose of study treatment, 27 fewer patients would experience a drug-related Grade 3–5 AE, but an additional 9 patients may experience a Grade 3, 4 or 5 immune-mediated AE. The risk of these immune-mediated events may be higher in clinical practice than that observed during the trial.

Interpretation of clinical evidence

Clinical claim and therapeutic relativity

6.24 The resubmission claimed that pembrolizumab is superior in terms of comparative effectiveness and superior in terms of comparative safety in patients with metastatic, previously untreated Stage IV NSCLC whose tumours express high levels of PD-L1 expression (TPS ≥50%) with no *EGFR* sensitising mutations or *ALK* translocations.

6.25 The PBAC previously accepted the claim of superior effectiveness of (for both PFS and OS) and superior safety of pembrolizumab compared with platinum-based doublet chemotherapy (Item 6.04, pembrolizumab PSD, March 2017 PBAC meeting). The extended OS data (with a median duration of follow-up of 19 months) presented in the pre-PBAC response to the March 2017 PBAC meeting, and in the current resubmission, remain immature.

6.26 The PSCR (p1, 9, 10) provided updated OS and PFS results for KN-024, and (p9) provided other trial results as "context" for the results from KN-024. The ESCs acknowledged the favourable OS results from the final analysis, however was concerned that the uncertainty around the estimate of incremental effect remained. The ESCs considered that a comparison of the OS results from KN-024 with those of other trials could not help resolve this concern.

6.27 When the PBAC considered the previous submission, the Committee considered that the comparative treatment effect of pembrolizumab versus chemotherapy with regard to improving QoL could not be reliably determined (Item 6.04, pembrolizumab PSD, March 2017 PBAC meeting). The resubmission did not provide any new clinical evidence to address this uncertainty.

Claim of codependence

6.28 The resubmission claimed that treatment guided by PD-L1 status, where patients with high tumour expression of PD-L1 (i.e. TPS ≥50%) are treated with pembrolizumab, and patients with low or no expression of tumour PD-L1 (i.e. TPS <50%) are treated with platinum-based doublet chemotherapy, results in improved outcomes versus the comparator, which is no testing and platinum-based doublet chemotherapy in all patients. This was based on the resubmission's conclusions that:

- the test is accurate,
- there is no prognostic impact of PD-L1 status (therefore patients with TPS ≥50% in the trial treated with platinum-based doublet chemotherapy can reasonably approximate an unselected population treated with platinum-based doublet chemotherapy),
- pembrolizumab has improved effectiveness and improved or non-inferior safety, when compared to platinum-based doublet chemotherapy, and
- that there is treatment effect variation by PD-L1 status.

6.29 The lack of a reference standard prevented the determination of the diagnostic accuracy of the Dako 22C3 assay. Thus, the proportions of false positives and false negatives could not be determined accurately. The clinical outcomes of treating the false positives have been captured in the KN-024 trial, but not those of not treating the false negatives. These patients would receive platinum-based doublet chemotherapy and may have inferior clinical outcomes compared with true positive patients receiving pembrolizumab. The PBAC noted that patients who are false negatives to the PD-L1 TPS (≥50%) test, and so do not qualify for pembrolizumab in the first-line setting, would be eligible to receive nivolumab in the second-line setting provided other restriction criteria for nivolumab are met.

6.30 Although the PFS and OS of patients with a TPS ≥50% treated with pembrolizumab is superior to that of those treated with chemotherapy, the comparative results in patients with a TPS <50% are unknown. If treatment effect modification is accepted, then the pembrolizumab treatment effect should increase as the level of PD-L1 expression increases. The selection of the 50% TPS threshold has not been justified as adequately discriminatory of a clinically relevant treatment effect. It is also unclear whether the results presented in KN-024 have been influenced by a biomarker-related prognostic effect given the uncertainty over the prognostic value of PD-L1.

Economic analysis

6.31 A modelled economic evaluation, with incremental cost per life-year gained and incremental cost per quality-adjusted life year (QALY) gained, was presented based on the claim of superior effectiveness and safety compared to platinum-based doublet chemotherapy in treatment-naïve NSCLC patients whose tumours expressed high levels of PD-L1 (TPS ≥50%).

Table 9: Summary of model structure and rationale

Component	Description	Justification/comments
Type of analysis	Cost-utility analysis (base case) Cost-effectiveness analysis	This is appropriate and unchanged from the previous submission.
Outcomes	QALYs LYG	These are appropriate health outcomes for a cost-utility analysis and a cost-effectiveness analysis, and unchanged from the previous submission.
Time horizon	7.5 years in the model base case (vs 19 months in KN-024)	The PBAC previously accepted a 5-year time horizon in the context of first-line treatment of NSCLC (afatinib, erlotinib and gefitinib PSDs, July 2013 PBAC meetings).
Methods used to generate results	Cohort analysis of partitioned survival (i.e. area under the curve)	This is reasonable and unchanged from the previous submission.
Health states	3 health states: progression-free, progressive disease and death	A 3-health-state economic model has often been used for cancer drugs. This is unchanged from the previous submission.
Cycle length	1 week	This is appropriate and unchanged from the previous submission.
Transition probability	PFS and OS data from KN-024 were the basis for determining the proportions of patients in each health state. The survival curves were extrapolated to the 7.5-year time horizon using parametric survival functions.	Updated OS data with extended follow-up (median: 19 months) were used in the economic model. However, the data remain immature for a reliable estimate of the long-term survival. The parametric distributions used for PFS and OS extrapolation remain unchanged from the previous submission. The PBAC has previously considered that the selection of a log-logistic distribution to extrapolate OS for pembrolizumab may be overly optimistic (Item 6.04, pembrolizumab PSD, March 2017 PBAC meeting).
Software package	Excel 2010	This is appropriate and unchanged from the previous submission.

NSCLC = non-small cell lung cancer; LYG = life-year gained; OS = overall survival; PFS = progression-free survival; PSD = public summary document; QALYs = quality-adjusted life-years
Source: Table 3.1-1, p192 of the resubmission

6.32 At the March 2017 meeting, "the PBAC considered the basic structure of the economic model was sound, but noted the various iterations of the economic evaluation from the submission, the PSCR and the pre-PBAC response, reflecting different assumptions and inputs which still adopt this basic structure." (paragraph 7.8, Item 6.04, pembrolizumab PSD, March 2017 PBAC meeting). In comparison with the March 2017 submission, the model structure in the resubmission remained the same, as did most of the inputs. The major changes in the model variables/assumptions between the two submissions are summarised below.

Table 10: Main differences in model inputs/assumptions between the previous and the current submissions

	March 2017 submission	Current resubmission
Time horizon	7 years[a]	7.5 years
OS estimates	Survival data from KN-024 with a median follow-up duration of 11 months (cross-over adjusted analysis)	Survival data from KN-024 with a median follow-up duration of 19 months (ITT analysis)
Adjustment for treatment switching?	Yes. Using two-stage approach in the base case	No
Drug acquisition costs	Based on the proposed and listed prices of each medicine at the time of previous submission	Updated using the proposed price for pembrolizumab and the current PBS prices for chemotherapies
Second-line immunotherapy upon disease progression considered?	No[b]	Yes: included second-line nivolumab following first-line platinum-based doublet chemotherapy
Costs for disease management	Based on the health care resource use data from the PIVOTAL study	Assumed reduced disease management costs in patients with stable disease for 2 years and in patients treated with pembrolizumab (vs chemotherapy).

[a] A 5-year time horizon was used in the pre-PBAC economic model relating to the previous submission.
[b] Second-line nivolumab in patients who have failed platinum-based doublet chemotherapy was not considered in the base case of the economic model in the previous submission, but was taken into account in the revised economic model in the pre-PBAC response.
Source: Table compiled during the evaluation, based on Section 3 of the resubmission and Section D of the previous submission.

6.33 A key difference arose because nivolumab was listed on the PBS on 1 August 2017 for treatment of patients with NSCLC who have progressed on or after prior platinum-based doublet chemotherapy. As the treatment switching from first-line platinum-based doublet chemotherapy to second-line immunotherapy as observed in KN-024 would now reflect Australian clinical practice, it is appropriate to use the ITT OS data, without adjustment for treatment switching, and to cost second-line nivolumab in the economic model. [redacted][4]). The resubmission assumed that patients would receive [redacted] 2-week cycles of nivolumab treatment after they have failed first-line platinum-based doublet chemotherapy. The estimation of the number of infusions for nivolumab in a second-line setting was not justified in the resubmission. KN-024 trial data on the duration of second-line immunotherapy following platinum-based doublet chemotherapy are lacking. The resubmission's assumption of a mean treatment duration of [redacted] may be an overestimate. An overestimated treatment duration for second-line nivolumab would result in an ICER/QALY favouring PD-L1/pembrolizumab.

6.34 The PSCR (p3) stated that the estimates of mean treatment duration with nivolumab were based on the nivolumab November 2016 PSD. The PSCR acknowledged that the treatment costs for nivolumab would need to be updated to reflect the Deed for nivolumab agreed with the Department if pembrolizumab was to receive a positive PBAC recommendation.

[4] The dispensed price for nivolumab was estimated by assuming that 29% of NSCLC patients would be treated in a public hospital setting and the remaining 71% in a private hospital setting (as assumed in the financial analysis of the resubmission).

6.35 The ESCs considered that patients enrolled in the later-line nivolumab for non-squamous NSCLC trial (Checkmate 057) were not representative of the subjects in KN-024, who experienced disease progression and received second-line nivolumab following first-line platinum-based doublet chemotherapy. The subjects in the nivolumab arm of Checkmate 057 appeared to have better prognosis than those in the chemotherapy arm of KN-024 at enrolment, e.g. with younger age (median age: 61 years vs 66 years) and more patients with less advanced disease (Stage IIIB disease: 7% vs 0.7%[5]) . The ESCs considered that it would be reasonable to assume that patients who progressed on or after first-line platinum-based doublet chemotherapy in KN-024 had a shorter time from first disease progression to subsequent disease progression compared with the PFS reported in Checkmate 057 and, thus, shorter duration of treatment with nivolumab. In KN-024, the median PFS and median time from randomisation to disease progression after second-line therapy or death (PFS2) were 6.1 months (Table 1, p9, PSCR) and 8.4 months (Figure 10, COM.116), respectively, for the platinum-based doublet chemotherapy arm, in which 64.2% of patients switched to a PD-1 inhibitor after progression. The difference (2.3 months) was much shorter than the [redacted] months assumed in the resubmission based on data from Checkmate 057. Sensitivity analyses were performed by reducing the number of treatment cycles from [redacted] to 5.0 cycles (i.e. 2.3 months) (Tables 13 and 14).

6.36 The pre-PBAC response (p2-3) argued that the approach applied by the ESCs to estimate the use of second-line nivolumab underestimated the treatment duration for two reasons:

- the PFS2 of 8.4 months is based on the entire ITT population, not just those that crossed over to a PD-1 inhibitor (64.2%); the treatment duration of the latter would be longer;
- the mean, rather than the median, treatment duration should be used to estimate costs, consistent with how costs were determined in the second-line nivolumab economic evaluation (November 2016 PSDs); this would be the best estimate of costs as it captures the subset of patients with durable responses.

The pre-PBAC response maintained that the [redacted] treatment duration for nivolumab proposed by the submission was appropriate.

6.37 The PBAC agreed with the ESCs' views on the treatment duration of second-line nivolumab, considering that:

- the health outcomes in the model reflected the 64.2% of trial participants crossing over to a PD-1 inhibitor, so if this basis were to be changed in estimating costs, corresponding change would be needed for estimating health outcomes, and
- the health outcomes in the model reflected an extrapolation from the truncated means in the clinical data, so in the absence of a similar

[5] Borghaei H, Paz‐Ares, L. Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. New England Journal of Medicine 2015; 373:1627-39

extrapolation for the truncated mean in the time to PFS2, the median is likely to provide a better estimate.

6.38 The key drivers of the model are summarised below.

Table11: Key drivers of the model

Description	Method/Value	Impact
Duration of pembrolizumab treatment	Treatment until disease progression or 2 years maximum.	If patients do not stop treatment at 2 years in practice, the assumption used in the model would favour PD-L1/pembrolizumab.
Extrapolation of pembrolizumab OS	The selection of the log-logistic model in the base case analysis may overestimate long-term survival.	High, favours PD-L1/pembrolizumab.
Time horizon	7.5 years	Moderate-high, favours PD-L1/pembrolizumab.
Duration of nivolumab treatment as a second-line therapy in no testing/chemotherapy arm	[redacted]	Moderate-high, favours PD-L1/pembrolizumab.

Source: Table compiled during the evaluation.

6.39 The result of the economic evaluation is summarised below, based on the submission's estimated cost of nivolumab, [redacted] (per 240 mg: [redacted] vs $5,165[6]).

Table 12: Results of the economic evaluation

Component		PD-L1/pembrolizumab	Platinum-based doublet chemotherapy	Increment
Costs		$[redacted]	$[redacted]	$[redacted]
LYs	Progression free	0.87	0.67	0.19
	Progressive	1.22	1.12	0.10
	Total	2.09	1.80	0.29
QALYs	Progression free	0.65	0.50	0.15
	Progressive	0.84	0.78	0.06
	Total	1.49	1.27	0.21
Incremental cost/extra LY gained				**$[redacted]**
Incremental cost/extra QALY gained				**$[redacted]**

LY = life year; PD-L1 = programmed cell death ligand 1; QALY = quality-adjusted life year.
Source: Table constructed during the evaluation, based on Table 3.8-4, p242 and Table 3.5-8, P243 of the resubmission and the 1L NSCLC Resubmission_Section 3 Workbook.xlsm.

The redacted table shows an ICER/LY in the range of $15,000/LY - $45,000/LY and an ICER/QALY in the range of $45,000/QALY - $75,000/QALY.

6.40 The result of the economic evaluation was subject to a number of assumptions. The PBAC considered that the main economic uncertainties were:

- the post hoc use of the Chow test;
- the extrapolation method of the trial OS curve for pembrolizumab; and

[6] The dispensed price for nivolumab was estimated by assuming that 29% of NSCLC patients would be treated in a public hospital setting and the remaining 71% in a private hospital setting (as assumed in the financial analysis of the resubmission).

- the treatment duration for nivolumab as second-line therapy in patients who have failed platinum-based doublet chemotherapy.

The economic model was sensitive to changes (and combination of changes) of the above variables (see the following table).

Table 13: Results of key sensitivity analyses based on the submission[c] (and PSCR[d])

		Incremental costs	Incremental QALYs	ICER
Base case		[redacted]	**0.21** ***(0.23)***	[redacted]
1	Parametric model to extrapolate OS for pembrolizumab (base case: log-logistic) • Exponential (best fit based on AIC and BIC)	[redacted]	0.17 *(0.19)*	[redacted]
2	Time horizon (base case: 7.5 years) • 5 years[a]	[redacted]	0.15 *(0.16)*	[redacted]
3	Cost for 2nd-line nivolumab [redacted] • Treatment duration of nivolumab calculated as median PFS2 minus median PFS[a, b]	[redacted]	0.21 *(0.23)*	[redacted]
Multivariate analyses[a]				
1+2	5-year time horizon + exponential extrapolation for pembrolizumab OS	[redacted]	0.14 *(0.15)*	[redacted]
1+2+3	5-year time horizon + exponential extrapolation for pembrolizumab OS + treatment duration of nivolumab calculated as median PFS2 minus median PFS[b]	[redacted]	0.14 *(0.15)*	[redacted]
1+3	Exponential extrapolation for pembrolizumab OS + treatment duration of nivolumab calculated as median PFS2 minus median PFS[b]	[redacted]	0.17 *(0.19)*	[redacted]

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; PFS2 = time from randomisation to disease progression after second-line therapy or death

[a] Sensitivity analyses performed during the evaluation

[b] Equals to 2.4 months (= 8.4 months – 6.0 months) based on the survival data presented in the resubmission (median follow-up of 11 months for PFS and 19 months for PFS2) and 2.3 months (= 8.4 months – 6.1 months) based on the updated survival data provided by the PSCR (median follow-up of 25 months for PFS and 19 months for PFS).

[c] Based on data with a median follow-up data of 19 months.

[d] Based on data with a median follow-up data of 25 months.

Source: Adapted from Table 3.9-4, p249 of the resubmission, including additional sensitivity analyses performed during the evaluation. (Source for figures in italics: Sensitivity analyses performed during the evaluation, based on the "Section 3 Workbook_Updated" Workbook provided with the PSCR)

The redacted table shows ICERs in the range of $45,000/QALY - $105,000/QALY.

6.41 Additional scenarios of test accessibility explored during the evaluation (compared to standard of care) are presented in the table below.

Table 14: Results of key sensitivity analyses based on the submission (and PSCR)

	ICER	ICER; Scenarios + multivariate analyses 1+2+3 of Table 13
Base case • MSAC funded test: testing at diagnosis of NSCLC (any stage) • Highly positive patients (TPS ≥50%) eligible for pembrolizumab • Maximum treatment duration for pembrolizumab course, 2 years	$[redacted]/QALY ($[redacted]/QALY)	$[redacted]/QALY
Scenario 1: Pembrolizumab treatment until progression	$[redacted]/QALY ($[redacted]/QALY)	$[redacted]/QALY
Scenario 2: Pembrolizumab eligibility not restricted by PD-L1 status (i.e. no testing)	$[redacted]/QALY[a] ($[redacted]/QALY) $[redacted]/QALY[b] ($[redacted]/QALY)	$[redacted]/QALY $[redacted]/QALY
Scenario 3: Testing of archived sample in patients who are diagnosed at an earlier stage of disease (Stage I-III)[c]	$[redacted]/QALY ($[redacted]/QALY)	$[redacted]/QALY
Scenario 4: Testing of re-biopsied material on diagnosis of advanced disease[d]	$[redacted]/QALY ($[redacted]/QALY)	$[redacted]/QALY

ICER = incremental cost effectiveness ratio; NSCLC = non-small cell lung cancer; QALY = quality-adjusted life year.

[a] As KN-024 did not enrol patients with TPS <50%, the resubmission estimated health outcomes in these patients with pembrolizumab treatment by assuming the efficacy of pembrolizumab in a PD-L1 negative cohort is the same as the efficacy of platinum-based doublet chemotherapy, as observed in KN-024

[b] As KN-024 did not enrol patients with TPS <50%, the resubmission estimated health outcomes in these patients with pembrolizumab treatment by assuming the efficacy of pembrolizumab in a PD-L1 negative cohort is halved compared with pembrolizumab in a PD-L1 positive cohort.

[c] Sample retrieval costs were applied in 48.5% of patients who received a diagnosis at an earlier stage of disease (based on an analysis of Victorian cancer registry data reported that 51.5% of NSCLC patients were Stage IV at diagnosis). A sample retrieval cost of $85.00 was applied, based on the MSAC advice when it considered MSAC Application 1331 (Review of archival tissue for further diagnostic testing) (Application 1331, public summary document, November 2016 MSAC meeting).

[d] A 48.5% re-biopsy rate was applied to reflect re-biopsy and subsequent testing in patients who received a diagnosis at earlier stage disease (based on an analysis of Victorian cancer registry data that reported that 51.5% of NSCLC patients were Stage IV at diagnosis).

Source: Constructed during the evaluation, based on the 1L NSCLC Resubmission_Section 3 Workbook.xlsm of the resubmission

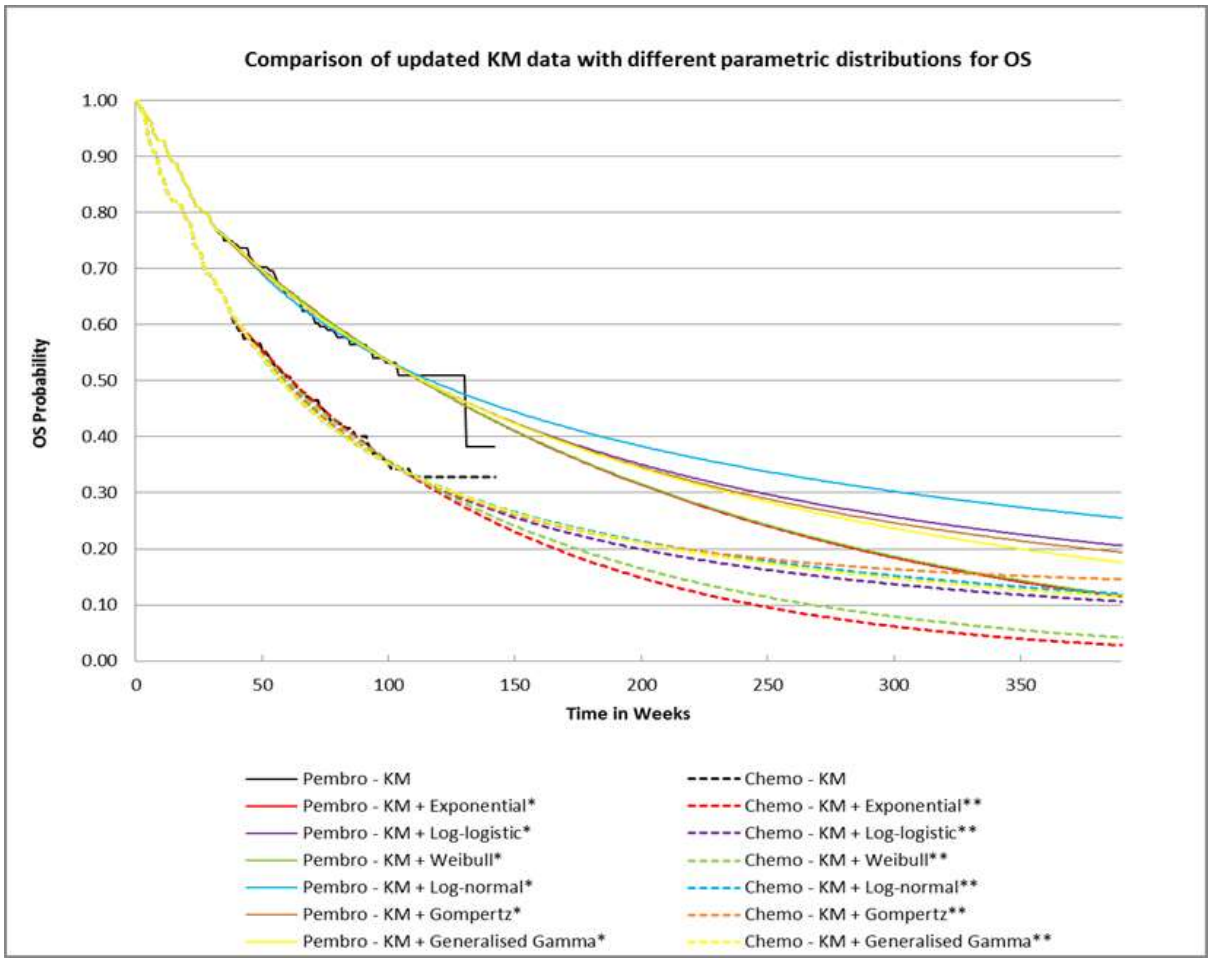
The redacted table shows ICERs in the range of $45,000/QALY - $200,000/QALY.

6.42 Compared to current care of platinum-based doublet chemotherapy without PD-L1 testing, the pembrolizumab all-comers strategy is associated with an ICER per QALY gained of $45,000 - $75,000 to more than $200,000, depending on different assumptions regarding the treatment effect of pembrolizumab in treatment of PD-L1 negative (TPS <50%) NSCLC. Given the ICERs per QALY gained were estimated using uncertain assumptions, the pembrolizumab all-comers funding strategy requires further clinical evidence before its cost-effectiveness can be explored further or established.

6.43 Treating patients with pembrolizumab until progression had a substantial impact on the ICER ([redacted]% increase). The resubmission indicated this uncertainty could be managed with a risk sharing arrangement (RSA) to be discussed further with the Department.

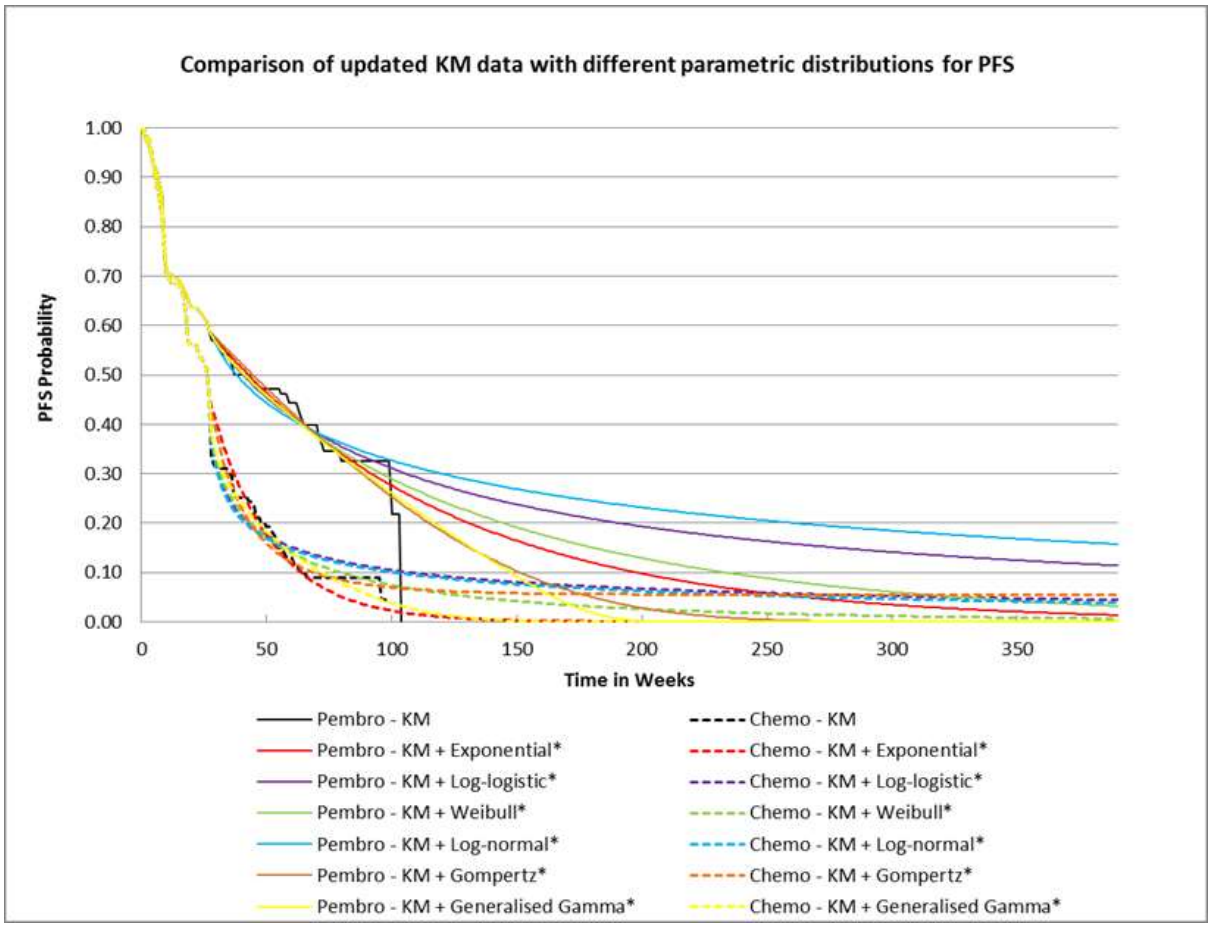
6.44 The ESCs noted that the PSCR provided a revised economic model that included the updated data from the KN-024 trial 10 July 2017 database lock. The ESCs noted that the Kaplan-Meier OS curve as presented in Figure 3 (p11) of the PSCR differed from the trial data provided with the revised economic model. The trial-based PFS and OS curves and the extrapolated curves are presented below.

Figure 3: Kaplan-Meier plot of OS for pembrolizumab (25 months median follow-up) fitted with different parametric distributions



* OS curve for pembrolizumab was extrapolated using different parametric distributions from Week 32
** OS curve for chemotherapy was extrapolated using different parametric distributions from Week 38
Source: constructed based on the "Section 3 Workbook_Updated" Workbook.

Figure 4: Kaplan-Meier plot of PFS for pembrolizumab (25 months median follow-up) fitted with different parametric distributions



* PFS curves for both pembrolizumab and chemotherapy were extrapolated using different parametric distributions from Week 27
Source: constructed based on the "Section 3 Workbook_Updated" Workbook.

6.45 The PBAC recalled (Item 6.04, pembrolizumab PSD, March 2017 PBAC meeting) that the selection of the log-logistic distribution to extrapolate OS for pembrolizumab in the economic model was optimistic. It was noted that the economic model in the pre-PBAC response to the March 2017 meeting used more conservative assumptions to estimate the survival benefits associated with pembrolizumab versus platinum-based doublet chemotherapy, i.e. a time horizon of 5 years and an exponential distribution to extrapolate the OS data for pembrolizumab. The extrapolation assumptions were tested in sensitivity analyses performed during the evaluation of the resubmission.

6.46 The PSCR (p11) then presented an updated OS Kaplan-Meier curve for patients receiving pembrolizumab to demonstrate the face validity of the extrapolation based on a log-logistic distribution, which the PSCR (p2) maintained was the appropriate basis for extrapolation. No other curves were fitted to the updated data and so it was not possible to assess the appropriateness of the log-logistic model. The PSCR also argued that the time horizon of 7.5 years was appropriate. The ESCs noted that, based on the updated model provided with the PSCR, 15.9% of patients in the pembrolizumab arm were modelled to be alive at 10 years, which the ESCs considered to be clinically implausible given the available clinical evidence and the

known prognosis of Stage IV NSCLC. The ESCs therefore considered that the selection of the log-logistic distribution for pembrolizumab lacked face validity.

6.47 The pre-PBAC response (p2) stated that, as the time horizon used in the economic evaluation is 7.5 years, the sponsor did not consider 10 year estimates relevant to the current analysis. The pre-PBAC response maintained that selection of the log-logistic function to extrapolate survival outcomes for pembrolizumab-treated patients was appropriate. The PBAC agreed with the ESCs that the log-logistic extrapolation for pembrolizumab alone was not appropriate, and considered that truncating the model at 7.5 years did not address the issue of clinical plausibility. The PBAC also agreed with the ESCs that using the more conservative exponential distribution for both interventions would have been more appropriate for the model as presented.

6.48 The ESCs noted that the start point of extrapolation used in the submission was 27 weeks for PFS, 32 weeks for pembrolizumab OS, and 40 weeks for chemotherapy OS; fractions of the available follow-up data. The ESCs advised that these start points were justified by the post hoc use of the Chow test, which the PBAC has previously advised in the context of this model was inappropriate for this purpose (see Table 9, pembrolizumab PSD, March 2017). Without also assessing the extrapolations using the full sets of observed data (i.e. starting at Day 1), the ESCs were unable to advise on the consequence of not using the earlier data in generating the extrapolations.

6.49 The PBAC agreed with the ESCs' views, considering that the approach taken in the modelling provided a further source of uncertainty in extrapolating the affected inputs to the economic evaluation from the clinical data.

Medicine cost/patient/course: $[redacted]

6.50 The average cost per administration was $[redacted] (4 x 50 mg vials). Each patient was assumed to have an average of [redacted] administrations per treatment course, based on the modelled time on treatment (e.g. patients would receive pembrolizumab until they experience disease progression or reach the maximum treatment duration of 2 years).

6.51 The resubmission estimated that the average cost for platinum-based doublet chemotherapy was $914, based on a cost of $183 per cycle for an average of five treatment cycles. The resubmission did not explain how the cost per cycle of $183 was calculated. The cost for platinum-based doublet chemotherapy with or without pemetrexed maintenance was estimated to be $897 per patient per course, by assuming:

- a weighted cost for platinum-based doublet chemotherapy of $103 per cycle (as used in the economic evaluation);
- an average of 4.25 administrations for platinum-based doublet chemotherapy, based on the economic model, applying the maximum of 5 treatment cycles;

- 11.5%[7] of patients receiving platinum-based doublet chemotherapy would continue onto pemetrexed maintenance;
- a cost for pemetrexed of $454 per cycle (as used in the economic evaluation); and
- a modelled treatment duration of 8.83 cycles for pemetrexed maintenance therapy.

The evaluation considered that these assumptions were reasonable.

Estimated PBS & financial implications

6.52 This submission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the number of patients eligible for pembrolizumab treatment each year over a 6-year period. The sponsor-commissioned ONCOSight report was used to estimate the incident patients with NSCLC. The number of patients eligible for pembrolizumab, i.e. patients with a performance status of 1 or 2 who are either diagnosed with Stage IV NSCLC or progress to Stage IV disease and whose tumours are *EGFR* wildtype *ALK* translocation negative and express ≥50% PD-L1, was estimated on the basis of the literature, clinical studies and previous PBAC/DUSC considerations. In estimating the net financial implications to the PBS/RPBS associated with the requested listing of pembrolizumab, there is uncertainty surrounding the disease progression rate from earlier stages of disease to Stage IV. Patients who would be eligible for pembrolizumab once PBS listing occurs via the grandfathering restriction in Year 1 of listing were also considered in the financial analysis. Given the claim of superior safety of pembrolizumab, the resubmission assumed a higher uptake rate for pembrolizumab than platinum chemotherapy (83.5%-85% vs 60%). The evaluation considered this was reasonable.

6.53 The PBS listing of pembrolizumab is expected to result in decreased use of current therapies used to treat the proposed target population, i.e. platinum-based doublet chemotherapy, most often gemcitabine and carboplatin, pemetrexed maintenance in some non-squamous patients, and second-line nivolumab.

6.54 The estimated financial impact of listing pembrolizumab is summarised in the table below.

[7] Based on data from the PIVOTAL study (Table 1b of Appendix 5 to the main submission).

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of pembrolizumab						
Number of patients likely to be treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of administrations[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of pembrolizumab to the PBS/RPBS						
Cost to PBS/RPBS less copayments[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for platinum-based doublet chemotherapy, pemetrexed maintenance and nivolumab						
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications to the PBS/RPBS						
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications to the MBS						
Net cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications to the Government						
Net cost to the Government	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised[c,d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] The average number of administrations per patient for pembrolizumab was based on the modelled time on treatment used in the economic evaluation, [redacted]

[b] Using the proposed effective price for pembrolizumab

[c] When calculating the number of patients who would be treated with second-line nivolumab, the resubmission erroneously multiplied the switching rate by the number of patients receiving first-line pembrolizumab, not the number of patients receiving platinum-based doublet chemotherapy. This error was revised during the evaluation.

[d] Estimates were revised during the evaluation by including costs for disease management and drug administration.

Source: Table 4.2-10, p261, Table 4.2-12, p263, Table 4.3-5, p267, Table 4.4-15, p275, Table 4.7-3, p283, and Table 4.5-2, p276 of the resubmission. Estimates in italics were calculated during the evaluation.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $30 - $100 million.

6.55 The decreased use of second-line nivolumab as a result of pembrolizumab listing was not considered in the previous submission, but was taken into account in the current resubmission. In estimating the cost offset associated with second-line nivolumab, the resubmission erroneously calculated the number of patients receiving second-line nivolumab by multiplying the switching rate (64.2%) by the number of patients likely to receive first-line pembrolizumab, not by the number of patients who would otherwise receive platinum-based doublet chemotherapy. After correcting this error, the nivolumab cost to the PBS/RPBS would decrease by around 29% compared to the submission's estimate. The cost-offset relating to second-line nivolumab was estimated to be $10 - $30 million in the first 6 years of listing, which accounted for about [redacted]% of the total cost-offsets associated with the listing of pembrolizumab. The inclusion of nivolumab following first-line platinum-based doublet

chemotherapy in the financial analysis would result in an increase in the proportion of the pembrolizumab cost to the PBS/RPBS offset by other medicines from [redacted]% - [redacted]% in the previous submission to [redacted]% - [redacted]% in the current resubmission.

6.56 The resubmission could have overestimated the cost-offsets associated with the proposed listing of pembrolizumab, as the treatment duration for platinum-based doublet chemotherapy and pemetrexed maintenance therapy used in the financial analysis was longer than the modelled time on treatment in the economic evaluation. The resubmission's assumption of 12 (2-week) cycles for nivolumab as second-line therapy following platinum chemotherapy is a likely overestimate. Using the modelled number of treatment cycles for platinum-based doublet chemotherapy and pemetrexed and reducing the duration of nivolumab treatment from [redacted] to 2.4 months[8] (5.2 cycles), the net cost to the PBS/RPBS would be $30 - $60 million per year in Year 1 of listing, increasing to $60 - $100 million per year in Year 6, based on the submission's estimated price of nivolumab.

6.57 Pembrolizumab use may displace rather than replace comparator platinum chemotherapy use. The exclusion of costs associated with second-line platinum-based doublet chemotherapy following first-line pembrolizumab in the financial analysis favours pembrolizumab. The PBAC considered that the cost of second-line chemotherapy should be accounted for in the financial analyses.

6.58 There is potential for pembrolizumab use in patients whose tumours express lower levels of PD-L1 (TPS <50%), particularly in those that weakly express PD-L1 (TPS 1-49%).

6.59 The PSCR (p7) stated that the cost to the PBS of treating patients with pembrolizumab was updated to take feedback from the evaluation into consideration. The PSCR provided a revised financial model, which was not independently verified.

Quality use of medicines

6.60 When the PBAC considered the previous submission, the Committee noted that a greater awareness, recognition and management of immune-related AEs was likely to have occurred in the KN-010 trial before AEs progressed to ≥ Grade 3. Until there is adequate familiarity with immunotherapy and its side effects, AE rates in practice may be higher than observed in the trial (Item 6.04, pembrolizumab PSD, March 2017 PBAC meeting). The resubmission noted that the sponsor will provide updated information to physicians, nurses, pharmacists and patients, education programs and a '1-800' telephone medical information service to ensure appropriate use of pembrolizumab including identifying and managing potential immune-related adverse events.

Financial management – risk sharing arrangements

6.61 The submission proposed a Special Pricing Arrangement (SPA).

[8] 2.4 months = 8.4 months – 6.0 months, where 8.4 months was the median time from randomisation to disease progression after second-line therapy in the platinum-based doublet chemotherapy arm in KN-024 (based on data with a median follow-up data of 19 months), and 6.0 was the median PFS.

6.62 The economic analysis and financial analysis were conducted by assuming patients still on pembrolizumab therapy would cease treatment at 2 years. The resubmission stated that a Deed of Agreement would be required if pembrolizumab is recommended, based on the administrations by treatment year to account for the costs associated with the patient at the appropriate time point.

6.63 The PBAC considered that a PBS listing of first-line pembrolizumab would impact on the Deed of Agreement for nivolumab. The PBAC considered that if pembrolizumab was made available on the PBS, there would only be a minor increase in the total number of patients treated for metastatic Stage IV NSCLC either in the first- or second-line setting, above what was estimated for the nivolumab caps at the time of negotiations with the sponsor of nivolumab. From first principles, the increase would comprise those patients with metastatic Stage IV NSCLC eligible in first-line who would otherwise not remain eligible in second-line, reduced by the proportion of first-line patients whose tumours do not express a high level of PD-L1 (i.e. have a TPS of <50%).

6.64 The PBAC advised that negotiations with the sponsor to determine the best approach for any RSA would need to be discussed in the context of the existing RSA for nivolumab in NSCLC.

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

7 PBAC outcome

7.1 The PBAC deferred making a recommendation to list pembrolizumab for the first-line treatment of patients with metastatic (Stage IV) non-small cell lung cancer (NSCLC), who do not have an activating epidermal growth factor receptor (*EGFR*) gene mutation or an anaplastic lymphoma kinase (*ALK*) gene rearrangement in tumour material, and whose tumours express high levels of programmed cell death ligand 1 (PD-L1), defined as a tumour proportion score (TPS) of ≥50%. In deciding to defer, the PBAC advised that (i) a further price reduction would be required for acceptable cost effectiveness once necessary changes are made to the economic evaluation; (ii) negotiations with the sponsor are required to determine the best approach for a Risk Sharing Agreement (RSA) in the context of the existing RSA for nivolumab in NSCLC; and (iii) updated advice is needed from the Medical Advisory Services Committee (MSAC) in relation to the codependent PD-L1 test. The PBAC also advised that, if MSAC subsequently decided to support the MBS listing for PD-L1, it would support the listing of pembrolizumab according to the circumstances supported by MSAC, once the PBAC's other concerns were resolved.

7.2 The PBAC noted that the revised restrictions provided in the resubmission appropriately addressed the Committee's previous concerns with regard to limiting the disease stage to Stage IV, performance status, and removing the eligibility for retreatment of patients who previously responded to treatment. The PBAC also agreed with the further changes suggested by the Secretariat for consistency with similar restrictions and to align the numbers of repeats with the maximum number of infusions allowed in the TGA-approved product information. The PBAC also foreshadowed that, in the event of any recommendation to list pembrolizumab, as

first-line therapy in metastatic NSCLC, both its restriction and that of nivolumab would need to be modified to prevent PBS-subsidised sequential immunotherapy.

7.3 The PBAC noted that, since its first consideration of pembrolizumab for first-line metastatic NSCLC in patients with TPS of ≥50% in March 2017, nivolumab (another PD-L1 inhibitor) has become PBS subsidised for the second-line treatment of NSCLC. The PBAC considered that this had shifted the clinical context and clinical need in the treatment of metastatic NSCLC, as patients whose tumours do not have high expression of PD-L1 and do not qualify for pembrolizumab in the first-line setting, may still access nivolumab in the second-line setting.

7.4 The PBAC noted that the resubmission provided no new evidence to justify the choice of the 50% TPS threshold as discriminatory for a clinically relevant variation in effect from pembrolizumab treatment. Similarly, the resubmission did not provide comparative evidence of the effectiveness of pembrolizumab in patients with tumour expression of PD-L1 TPS <50%. The PBAC considered that it is likely that pembrolizumab is effective in at least a proportion of these patients, although to a lesser extent than in those with a TPS ≥50%, if it is accepted that there is a link between increasing pembrolizumab treatment effect with increasing strength of PD-L1 expression. The PBAC also considered that there is the possibility of leakage in instances where patients' PD-L1 expression sits just below the TPS threshold, however, advised that this risk could be managed through an RSA. Additionally, the PBAC considered that patients whose tumours express TPS <50% and/or are false negatives and so would not qualify for first-line pembrolizumab still have the option of nivolumab in the second-line setting. Therefore, the PBAC considered that its concerns regarding the clinical utility of the PD-L1 test and the TPS threshold were of less clinical importance in the current clinical setting where nivolumab is available second-line, than at its March 2017 consideration of the pembrolizumab submission (where nivolumab was not available on the PBS). The PBAC foreshadowed that, in the event of a recommendation to list, the committee would propose changing the relevant criterion in the restriction to "Patient must have evidence of programmed cell death ligand 1 (PD-L1) expression in at least 50% of tumour cells in the tumour sample".

7.5 The PBAC agreed with the submission's nomination of platinum-based doublet chemotherapy as the main comparator for pembrolizumab in the proposed population. However, the PBAC also considered that pembrolizumab may displace rather than replace platinum-based doublet chemotherapy use.

7.6 The PBAC considered that the claims of superior comparative effectiveness (in terms of both progression-free survival and overall survival) and superior comparative safety were both reasonable. The PBAC considered that the trial data was robust, however noted that, although the median duration of follow up had increased to 25 months, less than half of the patients in the pembrolizumab arm died during the observation period. The OS data in the final analysis supplied in the PSCR, therefore, remained immature to estimate reliably the magnitude of long-term survival benefits of pembrolizumab versus platinum-based doublet chemotherapy in the proposed target population. The PBAC noted that approximately six patients would need to receive treatment with pembrolizumab for one additional survivor over two years. The PBAC noted that, overall, pembrolizumab is less toxic than platinum-based

doublet chemotherapy, but is associated with a higher risk of immune-mediated adverse events. The PBAC considered that autoimmune toxicities could be significant for a minority of patients, noting that, for approximately every 11 patients treated with pembrolizumab, there would be one case of Grade 3, 4 or 5 immune-mediated adverse event.

7.7 The PBAC recalled its consideration of the March 2017 submission that the data from KN-024 on quality of life were equivocal, and provided a weak basis to judge whether pembrolizumab resulted in no detriment to quality of life or possibly improved quality of life (Item 6.04, pembrolizumab PSD, March 2017 PBAC meeting). The PBAC noted the resubmission did not provide any new clinical evidence to address this uncertainty.

7.8 The PBAC noted the following key issues with the economic model identified by the ESCs.

- The post hoc use of the Chow test.
- The selection of a log-logistic distribution to extrapolate OS with pembrolizumab in the base case was not adequately justified as it was not the best fit for the clinical data or by Akaike Information Criterion or Bayesian Information Criterion. The use of log-logistic extrapolation resulted in an over-optimistic projected survival associated with pembrolizumab.
- The mean treatment duration for second-line nivolumab as assumed in the resubmission ([redacted]) was a likely overestimate. This favoured the strategy of testing for PD-L1 positivity (TPS ≥50%) and subsequent treatment of PD-L1 positive patients, compared with the current care (i.e. no PD-L1 testing + platinum-based doublet chemotherapy).

7.9 The PBAC recalled that it previously considered that that application of the Chow test would only be appropriate if the "structural changes" of the model slope were known a priori (pembrolizumab PSD, March 2017). Therefore, the PBAC considered that use of the Chow test was inappropriate in the context of the modelling, and that a consequence might have been to increase the modelled OS difference. The PBAC also considered that use of the Chow test to determine the start point of the goodness of fit comparison later in the Kaplan-Meier curve rather than from the start of the trial added a further source of uncertainty in extrapolating the affected inputs to the economic evaluation from the clinical data.

7.10 The PBAC agreed with the ESCs' view that the log-logistic extrapolation was not appropriate, and considered that truncating the model at 7.5 years did not address the issue of clinical plausibility. The PBAC advised that using the more conservative exponential distribution for both interventions would have been more appropriate for the model as presented.

7.11 The PBAC agreed with the ESCs' views on the treatment duration of second-line nivolumab, noting that:

- the health outcomes in the model reflected the 64.2% of trial participants crossing over to a PD-1 inhibitor, so if this basis were to be changed in

estimating costs, corresponding change would be needed for estimating health outcomes, and

- the health outcomes in the model reflected an extrapolation from the truncated means in the clinical data, so in the absence of a similar extrapolation for the truncated mean in the time to PFS2, the median is likely to provide a better estimate.

7.12 The PBAC noted that the ICER/QALY increased from $45,000/QALY - $75,000/QALY when the exponential function was used to extrapolate OS, and to $45,000/QALY - $75,000/QALY when the shorter treatment duration of nivolumab as proposed by the ESCs were applied in the economic model. The PBAC further noted that multivariate sensitivity analyses of these scenarios increased the ICER/QALY to $45,000/QALY - $75,000/QALY. The PBAC considered that, although use of the exponential function was a more conservative approach compared to the log-logistic function, there remained uncertainty in the economic model using an exponential function that still inappropriately excluded the earlier results of the relevant Kaplan-Meier curves. However, the PBAC decided to accept the submission's proposed time horizon of 7.5 years in light of other contextual issues identified below.

7.13 The PBAC considered that a further price reduction was required for any PBS listing of pembrolizumab to be acceptably cost-effective. The PBAC advised that the base case of the economic model would need to be respecified to:

- use the observed Kaplan-Meier results from the key trial in the model up to the median duration of follow-up;
- extrapolate the PFS and OS curves in the model beyond this time point with reference to parametric functions generated by appropriately using the observed Kaplan-Meier results for each treatment arm to inform their goodness of fit assessment (i.e. not excluding any Kaplan-Meier results by relying on the Chow test);
- apply the same extrapolation function between treatment arms for both PFS and OS;
- apply a conservative set of extrapolation curves after the median duration of follow-up that take into account the remaining uncertainty in the magnitude of PFS and OS benefit;
- converge the extrapolation curves to the base case time horizon of 7.5 years;
- estimate the duration of post-chemotherapy nivolumab use following the approach advised by the ESCs; and
- incorporate the effective price of nivolumab (in the case where pembrolizumab receives a positive PBAC recommendation so that the Deed of Agreement for nivolumab can then be disclosed to the sponsor of pembrolizumab).

7.14 The PBAC advised that the requested price for pembrolizumab should then be adjusted to maintain the ICER/QALY after these adjustments to the model to be less than $45,000/QALY - $75,000/QALY, given that the net costs to government are estimated to be high, at above $30 - $60 million per annum, and the large number of

patients with NSCLC. The PBAC considered that an acceptable ICER/QALY was critical to ensuring the cost effective listing of pembrolizumab and expected that the requested effective price of pembrolizumab would need to be reduced to achieve this target.

7.15 The PBAC also noted that increasing the average per patient cost of pembrolizumab by moving the recommended dose from a 2 mg/kg basis to a fixed 200 mg basis is likely associated with a 25% wastage of pembrolizumab[9] because corroborating evidence indicates that this is not also associated with an improvement in patient health outcomes. The PBAC considered that this further justified its expectation of a price reduction, given that the TGA has recommended dosing on a fixed basis.

7.16 The PBAC considered that the submission's estimates of substantial cost offsets from second-line nivolumab resulting from a PBS listing of first-line pembrolizumab in NSCLC would affect the risk sharing arrangements (RSA) in the Deed of Agreement for nivolumab in NSCLC. The PBAC considered that, if pembrolizumab was made available on the PBS, there would only be a minor increase in the overall number of patients treated for metastatic Stage IV NSCLC either in the first- or second-line setting, above what was accepted for the nivolumab caps at the time of the negotiations with the sponsor of nivolumab. However, as requested, the PBS listing of pembrolizumab would reduce the PBS expenditure on nivolumab, thus reducing the effect of its risk sharing arrangements, without necessarily providing similar risk sharing arrangements across both immunotherapies.

7.17 The PBAC advised that negotiations with the sponsor to determine the best approach for a RSA would need to be discussed in the context of the consequences for the existing RSA for nivolumab in NSCLC.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

MSD is disappointed that access to Keytruda has not yet been achieved for 1L NSCLC patients in Australia. MSD will continue to work with the Department to make this therapy available as soon as possible, so that Australian patients have comparable access to innovative NSCLC therapies as patients in other countries.

[9] JNCI J Natl Cancer Inst (2017) 109(11): djx063_JNCI J Natl Cancer Inst (2017) 109(11): djx063