

**6.05 PEMBROLIZUMAB,
Powder for injection 50 mg, 1 vial
Keytruda[®],
Merck Sharp & Dohme (AU) Pty Ltd.**

1 Purpose of submission

1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients who have evidence of high expression of programmed death ligand 1 (PD-L1), defined as a tumour proportion score (TPS) $\geq 50\%$.

2 Requested listing

2.1 The requested PBS listing is shown below. The requested listing is for patients who have evidence of high PD-L1 expression (TPS $\geq 50\%$).

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
PEMBROLIZUMAB 50 mg injection: powder for, 1 vial	240 mg	5 (initial) 7 (continuing)	\$ [REDACTED] (private) \$ [REDACTED] (public)	Keytruda [®] Merck Sharp & Dohme (AU) Pty Ltd

Treatment phase: initial treatment

Category / program:	Section 100 – Efficient funding of chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC
Treatment phase:	Initial treatment
Restriction level / method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

Public Summary Document – November 2016 PBAC Meeting

Clinical criteria:	<p>Treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>The condition must have progressed following treatment with a platinum-based chemotherapy agent unless contraindicated or not tolerated according to the TGA approved Product Information;</p> <p>AND</p> <p>The condition must have progressed following treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) (if eligible) unless contraindicated or not tolerated according to the TGA approved Product Information;</p> <p>AND</p> <p>The condition must have progressed following treatment with crizotinib (if eligible) unless contraindicated or not tolerated according to the TGA approved Product Information,</p> <p>AND</p> <p>The treatment must not exceed a total of 6 doses at a maximum dose of 2mg per kg every 3 weeks.</p>
Population criteria:	The patient must have evidence of high expression of programmed death ligand 1 (PD-L1), defined as 50% (or greater) positive cells by immunohistochemistry testing.
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.

Treatment phase: continuing treatment

Category / program:	Section 100 – Efficient funding of chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC
Treatment phase:	Continuing treatment
Restriction level / method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

Clinical criteria:	<p>Treatment must be the sole PBS-subsidised therapy for this condition</p> <p>AND</p> <p>Patient must have previously been issued with an authority prescription for this drug for this condition,</p> <p>AND</p> <p>Patient must have stable or responding disease.</p> <p>AND</p> <p>The treatment must not exceed a maximum dose of 2 mg per kg every 3 weeks.</p>
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- 2.2 Ongoing trials of pembrolizumab vs platinum-based chemotherapy in the first-line NSCLC setting (KN-042 and KN-024) are administering pembrolizumab as a 200 mg fixed dose regimen. Therefore a future change in dosage recommendations in NSCLC and across other indications is possible. The PBAC noted that the 2 mg/kg dose of pembrolizumab may be superseded by a flat dose of 200 mg, which would be higher than the average dose per patient based on 2 mg/kg dosing (i.e. 140 mg assuming a 70 kg patient), and thus increase the incremental cost effectiveness ratio (ICER) of pembrolizumab.

Alternative listing options

- 2.3 Eligibility for PBS-subsidised pembrolizumab was proposed to be dependent on high PD-L1 expression in tumour samples (TPS $\geq 50\%$). Patients with no evidence of PD-L1 expression (TPS $< 1\%$) or low PD-L1 expression (TPS 1–49%) were proposed to be ineligible. The sponsor expressed preparedness to consider a population whose tumours express TPS $\geq 1\%$ PD-L1 (that is, regardless of the level of PD-L1 expression), if it was deemed to be more appropriate for PBS listing. The key trial included in this submission (KN-010) only enrolled patients whose tumours expressed PD-L1 (TPS $\geq 1\%$), with the prespecified subgroup analysis of overall survival (OS) in the TPS $\geq 50\%$ stratum.
- 2.4 As PD-L1 expression is a continuum, nominating a threshold to reflect a “biomarker positive” TPS for a predictive effect was arbitrary and may change with evolving clinical data. The Pre-Sub-Committee Response (PSCR, p8) acknowledged that PD-L1 expression is a continuum, however it argued that the TPS $\geq 50\%$ point was clinically validated in the KN-010 trial and was not an arbitrary choice. The ESCs agreed with the commentary that the TPS $\geq 50\%$ threshold to be eligible for pembrolizumab treatment in NSCLC was arbitrary and considered that this threshold would exclude patients who express lower levels of PD-L1, but nonetheless would benefit from pembrolizumab treatment. The pre-PBAC response (p.3) stated that the TPS $\geq 50\%$ threshold was chosen to balance ease of implementation and improve the positive predictive value of the test while maintaining an acceptable negative predictive value, on the basis of the receiver operating characteristic (ROC) curve analysis. The PBAC expressed concerns about the rationale for using a TPS $\geq 50\%$ threshold simply on the basis that this point gives equal weight to sensitivity and specificity. The PBAC considered that alternative thresholds could be selected on the basis of different preferences for under- and over-treatment.
- 2.5 Two ongoing trials in the first-line NSCLC setting (KN-024 and KN-042) comparing pembrolizumab with platinum-based chemotherapies in treatment-naïve patients, only enrolled patients whose tumours express PD-L1. Similar to the KN-010 trial, the

KN-042 trial only enrolled patients with a PD-L1 TPS of $\geq 1\%$ (with the prespecified primary analysis also based on the PD-L1 TPS $\geq 50\%$ stratum). The KN-024 trial was restricted only to patients with a PD-L1 TPS of $\geq 50\%$.

- 2.6 The requested restriction did not specify performance status (PS), although the key trial only included patients with an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1. The PBAC considered that any PBS restriction would require that patients initiating on pembrolizumab would have a PS of 0 or 1.
- 2.7 The submission did not show that patients who fail a specific PD-L1 inhibitor would experience clinical benefit from another PD-1/PD-L1 inhibitor. The PBAC therefore considered that, if another PD-1/PD-L1 inhibitor became PBS-listed for NSCLC, any future restriction for pembrolizumab would need to state that the patient must not have received prior treatment with another PD-1/PD-L1 inhibitor for NSCLC.
- 2.8 The pre-PBAC response (p4) further proposed that patients should cease pembrolizumab after 35 administrations (approximately 2 years' duration of therapy), as per the KN-010 protocol, which would need to be reflected in the continuing treatment phase of any PBS restriction and reinforced in a risk sharing arrangement.

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

3 Background

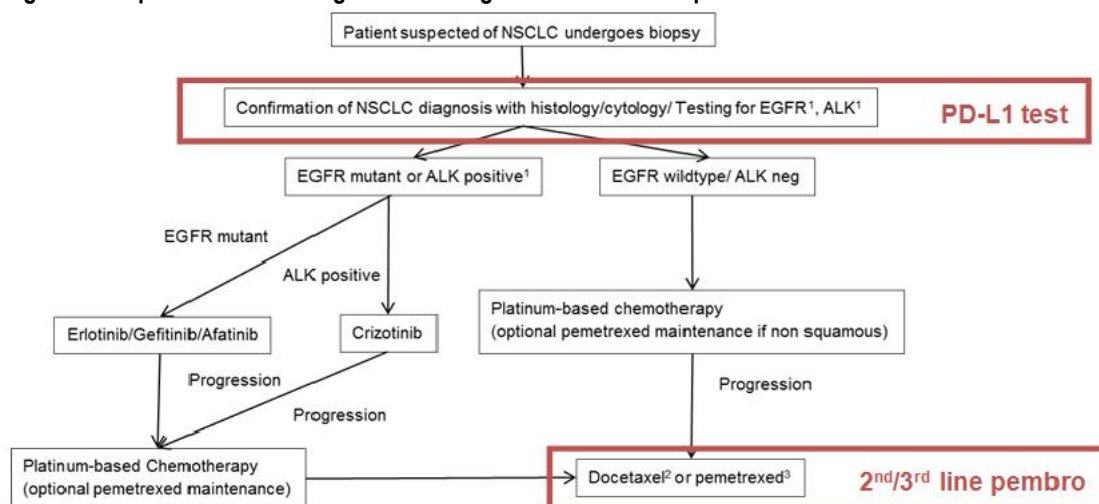
- 3.1 **TGA status at the time of PBAC meeting:** Pembrolizumab was approved by the TGA for unresectable or metastatic melanoma in April 2015. The sponsor submitted an application to the TGA under the TGA/PBAC parallel process to extend the indication for pembrolizumab for the treatment of NSCLC in the later-line setting. The TGA Delegate's Overview was not received by the time of the November 2016 PBAC meeting.
- 3.2 Pembrolizumab is currently PBS-subsidised for the treatment of unresectable Stage III or Stage IV malignant melanoma. This is the first consideration by the PBAC of pembrolizumab for the treatment of later-line NSCLC in patients who express PD-L1 at TPS $\geq 50\%$.
- 3.3 The submission to PBAC was part of an integrated codependent submission, which also included a submission to the Medical Services Advisory Committee (MSAC) for the codependent PD-L1 immunohistochemistry test, and thus was considered by a joint meeting of the PBAC's Economics Sub-Committee and MSAC's Evaluation Sub-Committee (the ESCs).

4 Clinical place for the proposed therapy

- 4.1 NSCLC comprises approximately 15%-25% of the squamous histologic subtype and 75%-85% of the non-squamous histologic subtype. The "non-squamous" subgroup includes adenocarcinoma and large cell carcinoma.

- 4.2 The proposed use of pembrolizumab is for 1) second-line treatment in patients who do not have EGFR mutations and would have progressed from first-line platinum-based chemotherapy (most squamous and some non-squamous patients) and 2) third-line treatment for the subset of non-squamous patients with specific genetic mutations such as EGFR mutations and ALK translocation (15-20%), who would have progressed following both first-line tyrosine kinase inhibitor (TKI) therapy and second-line platinum-based chemotherapy. Several other molecules which inhibit the PD-1/PD-L1 axis include nivolumab (another PD-1 inhibitor), atezolizumab and durvalumab (PD-L1 inhibitors).
- 4.3 The clinical management algorithm for the intended use of the PD-L1 test and pembrolizumab proposed by the submission is presented in Figure 1. The ESCs noted that the PSCR (p.1) confirmed that the intention is that testing would occur at the time of diagnosis, independent of stage of disease.

Figure 1: Proposed treatment algorithm in Stage IIIb/IV NSCLC for pembrolizumab and the PD-L1 test



ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand-1.

¹ Non-squamous or not otherwise specified histologies only

² Squamous or prior pemetrexed maintenance

³ Non-squamous if no prior maintenance therapy

Source: Figure A.5-2, p65 of the submission

5 Comparator

- 5.1 The submission nominated docetaxel as the main comparator for patients with squamous NSCLC and pemetrexed as the main comparator for patients with non-squamous NSCLC. This is consistent with previous PBAC considerations of nivolumab for both squamous and non-squamous NSCLC (March 2016) and of nintedanib (March 2015), crizotinib (November 2013) and erlotinib (July 2006) for non-squamous NSCLC.

- 5.2 Although pemetrexed as maintenance therapy in NSCLC has not been assessed as being cost-effective in NSCLC, this form of therapy with pemetrexed is currently used in clinical practice, as its use is not explicitly excluded by its PBS restriction and as

per recommendations in current Cancer Council Australia Guidelines^a. If patients have previously been treated with pemetrexed as maintenance therapy, it is likely that a different agent such as docetaxel would be used as the next line of chemotherapy. The KN-010 trial provides direct evidence for this comparison.

- 5.3 The PSCR argued that docetaxel is not supported as a main comparator in patients with non-squamous NSCLC, on the basis of the PBAC's views on the nivolumab submission (non-squamous NSCLC, March 2016) and results from an Australian observational study (PIVOTAL) undertaken in NSCLC patients initiated on therapy between 2011 and 2013. However, the PSCR also stated (p4) that, "in international jurisdictions access to pemetrexed has evolved in line with international clinical guidelines, and is now used first-line as part of a platinum doublet; consequently, docetaxel is the main second-line therapy that is used."
- 5.4 The ESCs noted that in some clinical settings, pemetrexed is used as maintenance therapy in non-squamous NSCLC and hence would be considered as part of first-line therapy following initial platinum-based chemotherapy. If a subsequent cycle of platinum-based chemotherapy with pemetrexed as maintenance were not to be used in this situation, then docetaxel might be used as the second-line therapy and so could also be a relevant comparator for patients with non-squamous NSCLC.
- 5.5 The PBAC considered that, consistent with its March 2016 consideration for nivolumab in the same patient setting, docetaxel and pemetrexed were the appropriate main comparators for patients with squamous and non-squamous NSCLC respectively.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented the rationale for selecting the PD-L1 expression threshold of 50%, and reiterated the submission's claim of overall survival benefit and superior safety profile with pembrolizumab treatment over chemotherapy. The clinician indicated that the TPS $\geq 50\%$ threshold was prospectively determined from a receiver operating characteristic (ROC) curve generated using data from the KN-001 trial.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from one individual and three organisations via the Consumer Comments facility on the PBS website. The comments described the clinical need for and value of treatments for patients with NSCLC.
- 6.3 The PBAC noted the input received from the Medical Oncology Group of Australia (MOGA) and the Lung Foundation of Australia, both providing strong support for

^a Australian Government Cancer Australia. Clinical practice guidelines for the treatment of lung cancer 2015 4 July 2016. Available from: http://wiki.cancer.org.au/australia/Guidelines:Lung_cancer

pembrolizumab. The MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for the PD-L1 TPS $\geq 50\%$ and TPS $\geq 1\%$ populations as 5 and 3 respectively (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)^[1], based on a comparison between pembrolizumab and docetaxel. The PBAC also noted the advice received from the Royal College of Pathologists of Australia (RCPA), which expressed concern regarding issues with the reproducibility, robustness and equivalence of PD-L1 testing using different PD-L1 antibodies across different assays. The RCPA also stated that PD-L1 expression had been shown to be inducible and dynamic, and that the RCPA do not endorse use of PD-L1 as a biomarker.

Clinical trials

6.4 The key features of the included evidence are summarised in Table 1. The trial protocol titles and citations of corresponding publications are summarised in Table 2.

Table 1: Key features of the included evidence

Trial	N	Design/ duration	Patient population	Outcome(s)	Use in modelled evaluation
Direct comparison between pembrolizumab and docetaxel in PD-L1 positive NSCLC					
KN-010	1034	R (1:1:1), OL, MC - pembrolizumab 2 mg/kg Q3W - pembrolizumab 10 mg/kg Q3W - Docetaxel 75 mg/m ² Q3W <u>Stratification:</u> by ECOG, region (east Asia vs non East Asia) and extent of PD-L1 expression (TPC 1–49% vs $\geq 50\%$). Treat for 24 months or until disease progression.	PD-L1 positive Stage IIIb/IV NSCLC who had progressive disease following platinum doublet and EGFR / ALK targeted therapy, if applicable	OS in PD-L1 positive (TPS $\geq 1\%$) and in PD-L1 strongly positive (TPS $\geq 50\%$) PFS in PD-L1 positive (TPS $\geq 1\%$) and in PD-L1 strongly positive (TPS $\geq 50\%$) Safety and tolerability in PD-L1 positive (TPS $\geq 1\%$) and in PD-L1 strongly positive (TPS $\geq 50\%$)	Used
Indirect comparison between KN-010 (pembrolizumab, PD-L1 positive) and Scagliotti (pemetrexed, non-PD-L1 selected) using docetaxel as the common reference					
Scagliotti et al, 2009.	571	Retrospective analyses (by histology subgroups) of a previously published trial (Hanna 2004). <u>Hanna:</u> R, OL - Pemetrexed 500 mg/m ² Q3W - Docetaxel 500 mg/m ² Q3W Median follow-up for all patients was 7.5 months.	Confirmed Stage III/IV NSCLC, progressive disease after treatment with 1 prior chemotherapy (not specified as platinum)	OS, ORR, CR.	Used

ALK = anaplastic lymphoma kinase; CR = complete response; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; MC = multi-centre; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q3W = every three weeks; R (1:1:1) = randomised 1 to 1 to 1 ratio; TPS = tumour proportion score. Source: compiled during the evaluation from the submission, KN-0101 clinical study report and Scagliotti and Hanna publications

^[1] Chery NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 26:1547-73, 2015

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial comparing pembrolizumab with docetaxel		
KN-010	<p>Clinical Study Report Protocol KN-010 A Phase II/III randomised trial of two doses of pembrolizumab/SCH900475 (pembrolizumab) versus docetaxel in previously treated subjects with NSCLC. CSR Identification P010V01. Database lock 23-Oct-2015.</p> <p><u>Publications</u> Herbst RS, Gurdip A, Summont V et al. A phase II/III randomised trial of two doses of pembrolizumab versus docetaxel in previously treated subjects with non-small cell lung cancer.</p> <p>Herbst, RS et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial.</p>	<p>Clinical Study Report. 10 December 2015</p> <p><i>Journal of Clinical Oncology</i>, 2014;32:5s (suppl; abstr TPS8124)</p> <p><i>The Lancet</i> 2015. December 19, 2015. Published online http://dx.doi.org/10.1016/S0140-6736(15)01281-7</p>
Indirect comparison between pembrolizumab and pemetrexed (common reference of docetaxel)		
<i>Proposed medicine: Pembrolizumab</i>		
KN-010	Refer to KN-010 above	
<i>Comparator: Pemetrexed</i>		
Hanna (2004)	Hanna N, Shepherd FA, Fossella FV et al. Randomised Phase III trial of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy.	<i>Journal of Clinical Oncology</i> , 2004; 22 (9): 1589-1597.
Scagliotti (2009)	Scagliotti G, Hanna, N, Fossella, F et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies.	<i>The Oncologist</i> , 2009; 14: 253-263
	Scagliotti G, Brodowicz T, Shedherd FA et al. Treatment by histology interaction analyses in three phase III trials show superiority of pemetrexed in non-squamous non-small cell lung cancer.	<i>J Thorac Oncol</i> , 2011; 6(1) 64-70

Source: Tables B.1.3 and B.1.6, pp73-8 of the main submission

- 6.5 The overall risk of bias associated with the included evidence is summarised in Table 3.

Table 3: Overall risk of bias associated with the included evidence

	Overall risk of bias in clinical trials
Direct comparison between pembrolizumab and docetaxel KN-010 (randomisation was stratified by TPS 1–49% vs TPS ≥50%)	<p>ITT (TPS >1%): Low risk of bias for outcome of OS (No treatment switching from docetaxel to pembrolizumab was permitted). High for adverse events and quality of life (open-label)</p> <p>Squamous TPS ≥50% subgroup: High risk of bias and imprecision for all outcomes due to small sample size and imbalances in baseline characteristics.</p>
Indirect comparison between pembrolizumab and pemetrexed using docetaxel as the common reference.	<p>Only exploratory non-squamous subgroup analysis available High risk of bias for all analyses. Data for pemetrexed were sourced from retrospective analyses of histology subgroups (Scagliotti 2009) from the previously published trial (Hanna 2004). There are important transitivity concerns with the indirect comparisons which include baseline disease characteristics and time lag between the KN-010 trial and the Hanna trial.</p>

ITT = intention-to-treat; OS = overall survival; TPS = tumour proportion score.

Source: Constructed during the evaluation

Comparative effectiveness

Direct comparison between pembrolizumab and docetaxel

- 6.6 As there was minimal confounding of OS by treatment switching (as per the trial protocol), the OS results were the primary and more relevant analyses of treatment effectiveness.
- 6.7 The OS results from the KN-010 trial for the ITT population (all PD-L1 positive, TPS ≥1%), and for the weakly (TPS 1–49%) and strongly (TPS ≥50%) PD-L1 positive subgroups are presented in Table 4. The Kaplan-Meier curves for the ITT population are presented in Figure 2. Although the proposed dose of pembrolizumab is 2 mg/kg in the draft Product Information, the TGA has yet to make a decision about the recommended dose of pembrolizumab in NSCLC.

Table 4: KN-010: OS analysis by PD-L1 expression levels (data cut-off: 30 September 2015). Note: randomisation was stratified by TPS 1–49% vs ≥50%

Population (Regardless of histology)	Pembrolizumab dose, Q3W	Pembrolizumab n with event/N (%) Median OS months (95% CI)	Docetaxel 75 mg/m ² , Q3W n with event/N (%) Median OS months (95% CI)	HR (95% CI) [†] Pembrolizumab vs docetaxel
ITT population, TPS ≥1% (all PD-L1 positive)	2 mg/kg	172/344 (50.0) 10.4 (9.4, 11.9)	193/343 (56.3) 8.5 (7.5, 9.8)	0.71 (0.58, 0.88)
	10 mg/kg	156/346 (45.1) 12.7 (10.0, 17.3)		
Subgroup, TPS ≥50% (strongly PD-L1 positive)	2 mg/kg	58/139 (41.7) 14.9 (10.4, NR)	86/152 (56.6) 8.2 (6.4, 10.7)	0.54 (0.38, 0.77)
	10 mg/kg	60/151 (39.7) 17.3 (11.8, NR)		
Subgroup, TPS 1–49% (weakly PD-L1 positive)	2 mg/kg	114/205 (55.6) 9.4 (8.7, 10.5)	107/191 (56.0) 8.6 (7.8, 9.9)	0.79 (0.61, 1.04)
	10 mg/kg	96/195 (49.2) 10.8 (8.9, 13.3)		

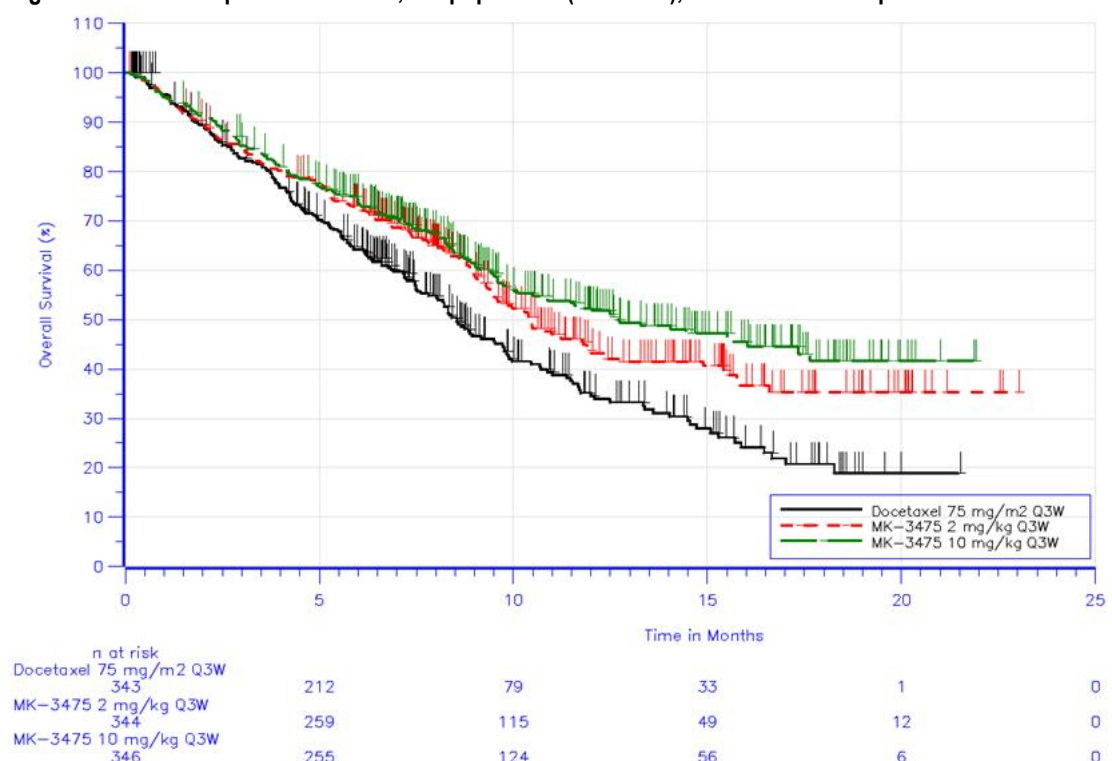
Test for treatment effect variation between strong and weak expression TPS ≥50% vs TPS 1–49%	Pembrolizumab 2mg/kg vs doc	Pembrolizumab 2 mg/kg vs docetaxel in ≥50% versus Pembrolizumab 2 mg/kg vs docetaxel in 1–49% Ratio of HRs (95% CI): [redacted] ([redacted], [redacted]); p = [redacted]
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¹ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), geographic region (East Asian vs. non-East Asian), and PD-L1 status by TPS.

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; NR = not reported (assumed for the evaluation as “not reached”); Q3W = every three weeks; PD-L1 = programmed death ligand 1; TPS = tumour proportion score (% of tumour cells staining for PD-L1 expression).

Sources: Data for the 1–49% were sourced from Table 14.2.1-7, p666 of the KN-010 clinical study report. The approach by Altman et al (2003)^b was used to conduct tests for treatment effect variation during the evaluation. Data for all other PD-L1 expression strata from Tables B.6.1 (p109) and B.6.3 (p111) of the main submission.

Figure 2: KN-010: Kaplan-Meier of OS, ITT population (TPS ≥1%), data cut-off: 30 September 2015



ITT = intention-to-treat; TPS = tumour proportion score (% of tumour cells staining for PD-L1 expression); MK-3475 = Pembrolizumab; Q3W = every three weeks.

Source: Figure B.6.3, p116 of the main submission

- 6.8 Pembrolizumab 2 mg/kg was statistically significantly superior compared with docetaxel for the ITT population (all PD-L1 positive, TPS ≥1%: 30% reduction in risk of death) and the subgroup who were strongly PD-L1 positive (TPS ≥50%: 50% reduction in risk of death), when histology was not considered. The TPS ≥1% results were likely driven by the strongly PD-L1 positive subgroup. In the weakly PD-L1 positive subgroup (TPS 1–49%), the gain in OS favouring pembrolizumab over docetaxel was statistically significant only for the pembrolizumab 10 mg/kg dose.

^b Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ*. 2003;326(7382):219.

- 6.9 The median OS gain with pembrolizumab over docetaxel was substantially larger for the TPS $\geq 50\%$ subgroup (6.7 months and 9.1 months for the pembrolizumab 2 mg/kg and 10 mg/kg doses, respectively) compared with the TPS 1–49% subgroup (1-2 months). A test for treatment effect variation for the prespecified strong (TPS $\geq 50\%$) vs weak (TPS 1–49%) expression subgroups was not statistically significant ($p = \blacksquare$), possibly due to inadequate statistical power. The incremental gain in median survival of pembrolizumab over docetaxel was largest for the TPS $\geq 50\%$ subgroup and that using this result rather than the result for the ITT population had a large and favourable impact on the ICER.
- 6.10 Patients randomised to the pembrolizumab 10 mg/kg arm of the trial experienced longer median OS compared to those randomised to the pembrolizumab 2 mg/kg arm (e.g. in the TPS $\geq 50\%$ subgroup, 17.3 months [pembrolizumab 10 mg/kg] versus 14.9 months [pembrolizumab 2 mg/kg] versus 8.2 months [docetaxel]).
- 6.11 The ESCs noted that, based on the test for treatment effect variation between strong and weak PD-L1 expression (TPS $\geq 50\%$ vs TPS 1–49%), there was inconclusive evidence that strong PD-L1 expressers responded better to pembrolizumab than weak PD-L1 expressers. The pre-PBAC response (Figure 1, p7) maintained that, in KN-010, the overall response rate to pembrolizumab was greater at the higher PD-L1 expression levels, compared to docetaxel.
- 6.12 The PBAC considered that, although the trial data suggested that there was likely to be treatment effect variation by intensity of PD-L1 expression, the application of these trial results to the Australian context required confidence in the trial’s approach to testing of the biomarker. The PBAC proposed to await MSAC’s advice on this matter. In addition, the PBAC noted that the 50% threshold was weakly supported, and would likely exclude patients who would benefit to a lower extent. The PBAC therefore concluded that selecting an appropriate PD-L1 expression threshold to determine eligibility to receive pembrolizumab remained problematic.
- 6.13 The OS results from the KN-010 trial, in the ITT population and TPS $\geq 50\%$ subgroup, by histology subtype, and tests for treatment effect variation (ratio of HRs) between squamous and non-squamous histotypes, are presented in Table 5.

Table 5: KN-010: OS analysis by histology subtype and TPS threshold (data cut-off: 30 September 2015). Note: randomisation was not stratified by histology subtype

Population	Pembrolizumab 2 mg/kg Q3W n=number of subjects Median OS, months (95% CI)	Docetaxel 75 mg/m ² Q3W n=number of subjects Median OS, months (95% CI)	HR (95% CI) Pembrolizumab vs docetaxel
ITT population, TPS $\geq 1\%$			
Squamous	n= [] [] ([], [])	n= [] [] ([], [])	[] ([], [])
All non-squamous (adenocarcinoma, large-cell and other)	n= [] [] ([], [])	n= [] [] ([], [])	[] ([], [])
Test for treatment effect variation All non-squamous Vs squamous	Pembrolizumab 2 mg/kg vs docetaxel in all non-squamous <u>versus</u> Pembrolizumab 2 mg/kg vs docetaxel in squamous Ratio of HRs (95% CI): [] ([], []); p = []		

Subgroup, TPS ≥50%			
Squamous			
All non-squamous (adenocarcinoma, large-cell and other)			
Adenocarcinoma non-squamous only			
Test for treatment effect variation All non-squamous Vs squamous	Pembrolizumab 2 mg/kg vs docetaxel in all non-squamous versus Pembrolizumab 2 mg/kg vs docetaxel in squamous Ratio of HRs (95% CI): [redacted] ([redacted], [redacted]); p = [redacted]		
Test for treatment effect variation Adenocarcinoma non-squamous Vs squamous	Pembrolizumab 2 mg/kg vs docetaxel in adenocarcinoma versus Pembrolizumab 2 mg/kg vs docetaxel in squamous Ratio of HRs (95% CI): [redacted] ([redacted], [redacted]); p = [redacted]		

– = not reached; CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival; PD-L1 = programmed death ligand 1; Q3W = every three weeks; TPS = tumour proportion score.

Source: Table B.6-37, p168 of the submission and Appendix 15 of the main submission. Interaction analyses were conducted during the evaluation using the approach by Altman et al (2003)

- 6.14 In the squamous subgroup of the TPS ≥50% subgroup, the gain in median OS of [redacted] months for pembrolizumab 2 mg/kg over docetaxel was not statistically significant. The clinical benefit of pembrolizumab in the squamous subgroup remains inconclusive, requiring cautious interpretation taking into consideration the small subgroup sample size. The results were similar in the larger squamous NSCLC subgroup of the TPS ≥1% (ITT) population, with no statistically significant difference in OS between pembrolizumab and docetaxel (HR = [redacted]; 95% CI [redacted], [redacted]).
- 6.15 In the non-squamous subgroup, pembrolizumab 2 mg/kg was associated with a statistically significant gain in OS over docetaxel in terms of both median OS gain ([redacted] months) and the relative hazard (HR = [redacted]; 95% CI [redacted], [redacted]). There was also a statistically significant gain in OS associated with pembrolizumab 10 mg/kg compared with docetaxel (HR = [redacted]; 95% CI [redacted], [redacted]). The median OS was not reached at the September 2015 data cut-off.
- 6.16 The submission acknowledged the limited statistical power of the squamous subgroup, but argued (p162 of the submission) that there was “no statistical evidence of heterogeneity with regard to the hazard ratios between squamous patients and the complement group (patients with Histology Other than Squamous)”. The submission based the clinical claim for squamous NSCLC on results encompassing both non-squamous and squamous results from KN-010.
- 6.17 Tests for treatment effect variation (ratio of HRs) between the squamous and non-squamous histotypes were not statistically significant, either for the ITT (TPS ≥1%) population (ratio of HRs = [redacted]; 95% CI: [redacted], [redacted]), or for the narrower TPS ≥50% subgroup (ratio of HRs = [redacted]; 95% CI: [redacted], [redacted]). Analyses based on the small squamous subgroup have limited statistical power and any conclusion regarding clinical heterogeneity across the histology subgroups should be regarded with caution.
- 6.18 The PSCR presented updated data from KN-010, which included an extra six months of follow-up compared to the data in the submission (data cut-off: 31 March 2016). The updated OS results from the KN-010 trial for the TPS ≥50% subgroup is

presented in Table 6 and Figure 3. Updated OS results for the ITT population (TPS $\geq 1\%$) were not provided in the PSCR.

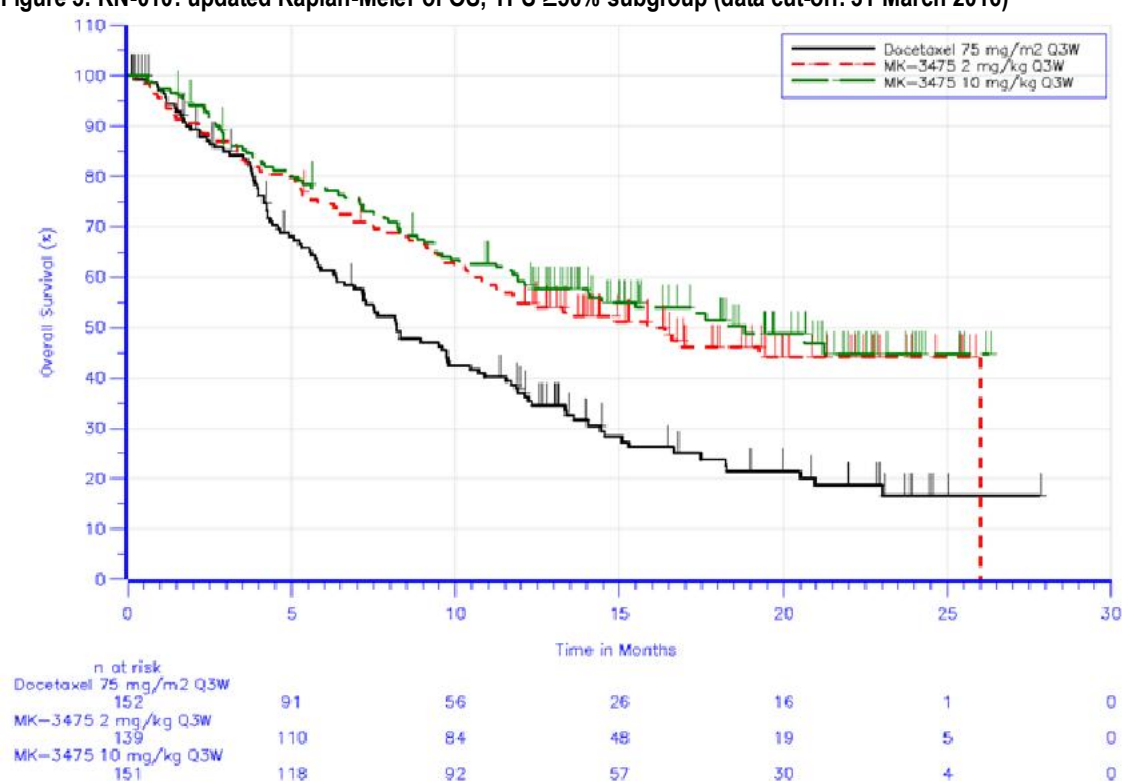
Table 6: KN-010: updated OS analysis for the TPS $\geq 50\%$ subgroup (data cut-off: 31 March 2016)

Treatment	N	Median OS months (95% CI)	HR (95% CI) Pembrolizumab vs docetaxel	p-value
Docetaxel 75 mg/m ² Q3W	151	8.2 (6.6, 10.4)	-	-
Pembrolizumab 2 mg/kg Q3W	139	15.8 (11.0, 26.0)	0.54 (0.39, 0.73)	0.00004
Pembrolizumab 10 mg/kg Q3W	139	18.8 (12.3, NR)	0.48 (0.35, 0.66)	<0.00001

CI = confidence interval; HR = hazard ratio; NR = not reported; Q3W = every three weeks; TPS = tumour proportion score (% of tumour cells staining for PD-L1 expression).

Source: Table 1, p9 PSCR

Figure 3: KN-010: updated Kaplan-Meier of OS, TPS $\geq 50\%$ subgroup (data cut-off: 31 March 2016)



TPS = tumour proportion score (% of tumour cells staining for PD-L1 expression); MK-3475 = Pembrolizumab; Q3W = every three weeks.

Source: Figure 1, p11 PSCR

- 6.19 The PSCR (p5) stated that, based on the updated data from KN-010, there was no difference in OS (or PFS) between the pembrolizumab 2 mg/kg and 10 mg/kg doses, and that future trials for pembrolizumab use a flat 200 mg dose regimen.
- 6.20 The ESCs noted that, in the TPS $\geq 50\%$ subgroup, there was no statistically significant difference in OS between the pembrolizumab 2 mg/kg and 10 mg/kg doses, and that pembrolizumab was superior over docetaxel in OS. The ESCs noted that the PSCR did not provide subgroup analyses by histology or an updated indirect comparison of pembrolizumab with pemetrexed.

- 6.21 The ESCs requested that updated OS results from KN-010 for the ITT (TPS ≥1%) population stratified by histology (all squamous and all non-squamous) be provided by the sponsor in the pre-PBAC response.
- 6.22 The pre-PBAC response presented updated data from KN-010 for the ITT (TPS ≥1%) population shown in Table 7; however, the data were not stratified by histology.

Table 7: KN-010: updated OS analysis for the ITT (TPS ≥1%) population (data cut-off: 31 March 2016)

Treatment	N	Median OS months (95% CI)	HR (95% CI) Pembrolizumab vs docetaxel	p-value
Docetaxel 75 mg/m ² Q3W	343	8.6 (7.9, 9.8)	-	-
Pembrolizumab 2 mg/kg Q3W	344	10.5 (9.6, 12.4)	0.72 (0.60, 0.87)	0.00030
Pembrolizumab 10 mg/kg Q3W	346	13.6 (11.4, 17.3)	0.60 (0.50, 0.73)	<0.00001

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; Q3W = every three weeks; TPS = tumour proportion score (% of tumour cells staining for PD-L1 expression).

Source: Table 1, p3 pre-PBAC response

- 6.23 The OS results from Trial KN-010 by PD-L1 expression levels and by histology subtype is presented in Table 8.

Table 8: KN-010: Patients with TPS ≥50% vs TPS 1–49%: OS analysis by histology subtype (data cut-off: 30 September 2015). Note: randomisation was not stratified by histology subtype

Population (by histology subtype)		Pembrolizumab 2 mg/kg Q3W n=number of subjects Median OS, months (95% CI)	Docetaxel 75 mg/m ² Q3W n=number of subjects Median OS, months (95% CI)	HR (95% CI) Pembrolizumab vs docetaxel
Squamous	TPS ≥50%	n= [Forest Plot]	n= [Forest Plot]	[Forest Plot]
	TPS 1–49%	n= [Forest Plot]	n= [Forest Plot]	[Forest Plot]
Adenocarcinoma non-squamous only	TPS ≥50%	n= [Forest Plot]	n= [Forest Plot]	[Forest Plot]
	TPS 1–49%	n= [Forest Plot]	n= [Forest Plot]	[Forest Plot]
Test for treatment effect variation	Squamous TPS ≥50% Vs Squamous TPS 1–49%	Pembrolizumab 2 mg/kg vs docetaxel in squamous TPS ≥50% Vs Pembrolizumab 2 mg/kg vs docetaxel in squamous, TPS 1–49% Ratio of HRs (95% CI): [Forest Plot]; p = 0 [Forest Plot]		
	Adenocarcinoma non-squamous TPS ≥50% Vs Adenocarcinoma non-squamous TPS 1–49%	Pembrolizumab 2 mg/kg vs docetaxel in adenocarcinoma TPS ≥50% Vs Pembrolizumab 2 mg/kg vs docetaxel in adenocarcinoma, TPS 1–49% Ratio of HRs (95% CI): [Forest Plot], p = 0 [Forest Plot]		
Test of whether the PD-L1 predictive effect varies between non-squamous and squamous subgroups		Predictive effect of PD-L1 status in non-squamous 0.63 (0.37, 1.10) Vs Predictive effect of PD-L1 status in squamous 1.10 (0.41, 2.97) Ratio of HR ratios (95% CI): [Forest Plot]		

– = not reached; CI = confidence interval; doc = docetaxel; HR = hazard ratio; NR = not reported; PD-L1 = programmed death ligand 1; Q3W = every three weeks; TPS = tumour proportional score.

The approach by Altman et al (2003) was used to conduct tests for treatment effect variation during the evaluation.

Sources: Table 14-12, pp615-618, Figure 14.2.5-5, p812 and Figure 14.2.5-6, p813 of the KN-010 CSR; Table 9, pp50-55; Table 26, p97 and Table 30, p101 Appendix 15 to the submission

- 6.24 PD-L1 treatment effect modification (TPS $\geq 50\%$ vs TPS 1–49% expression) was not statistically significantly different between non-squamous vs squamous histology subtypes although the effect modification appeared more convincing for non-squamous NSCLC. These analyses are substantially limited by the small sample size of the squamous subgroup.
- 6.25 The PBAC noted that the KN-010 trial was not statistically powered to detect a difference between pembrolizumab and docetaxel by histology subgroups and that patients with squamous NSCLC formed only 21% of the ITT trial population. The PBAC considered that the effectiveness of pembrolizumab was likely to be similar for both squamous and non-squamous PD-L1 positive NSCLC, but that the incremental effectiveness would vary due to the different comparators across these histology subgroups.

Indirect comparison between pembrolizumab and pemetrexed for non-squamous NSCLC

- 6.26 Table 9 summarises the results of the indirect comparison between pembrolizumab (PD-L1 TPS $\geq 50\%$) and pemetrexed (unselected for PD-L1 expression) with docetaxel as the common reference in non-squamous NSCLC (including large-cell and adenocarcinoma subtypes).

Table 9: OS: Indirect comparison of pembrolizumab (PD-L1 $\geq 50\%$) vs pemetrexed (unselected PD-L1) in all non-squamous NSCLC patients

	Pembrolizumab ^a 2 mg/kg, PD-L1 $\geq 50\%$ KN-010 trial		Pemetrexed trial Unselected for PD-L1 Scagliotti (2009) ^b		Indirect treatment effect Pembrolizumab vs pemetrexed
	Pembrolizumab	Docetaxel	Pemetrexed	Docetaxel	
N			205	194	
Number of events (%)			Not reported	Not reported	
Median, months, (95% CI)	15.8 (10.4, –)	8.2 (6.3, 10.7)	9.3 (7.8, 9.7)	8.0 (6.3, 9.3)	
HR (95% CI)	0.47 (0.31, 0.70)		0.78 (0.61, 1.00)		0.60 (0.37, 0.97)

^a Non-squamous sub-group

^b Retrospective analysis of non-squamous subgroup from Hanna (2004)

– = not reached; CI = confidence interval; HR = hazard ratio; PD-L1 = programmed death ligand 1.

Source: Table B.6-35, p164 and Table C.2-10, p269 of the Pembrolizumab submission; Table 4, p258 and Figure 2, p259 Scagliotti (2009)

- 6.27 Pembrolizumab 2 mg/kg was associated with a statistically significant gain in OS over pemetrexed (HR = 0.60; 95% CI (0.37, 0.97)). The median OS in the pembrolizumab arm was approximately 16 months compared to 9 months in the pemetrexed arm with approximately 8 months in the docetaxel arms. An indirect analysis using all PD-L1 positive (TPS $\geq 1\%$) non-squamous patients did not show a clear gain in OS associated with pembrolizumab over pemetrexed (HR = 0.86; 95% CI 0.61, 1.21).
- 6.28 The submission also presented an additional indirect comparison between pembrolizumab and pemetrexed using a narrower adenocarcinoma subgroup from both the KN-010 and Scagliotti datasets. The justification was that the composition of the non-squamous population was “heterogeneous” in terms of large cell histology which favoured pemetrexed over docetaxel in the Scagliotti dataset. For patients in

Scagliotti who had “other than Squamous” histology, 75% and 12% had adenocarcinoma and large cell carcinoma subtypes, respectively. These proportions were different in the KN-010 PD-L1 TPS $\geq 50\%$ dataset (■% and ■%, respectively). The results are summarised in Table 10.

Table 10: Overall Survival: Indirect comparison of pembrolizumab (PD-L1 $\geq 50\%$) vs pemetrexed (unselected PD-L1) in patients with adenocarcinoma only NSCLC

	Pembrolizumab ^a 2 mg/kg, PD-L1 $\geq 50\%$, KN-010 trial		Pemetrexed trial Unselected for PD-L1 Scagliotti (2009) ^b		Indirect treatment effect Pembrolizumab vs pemetrexed
	Pembrolizumab	Docetaxel	Pemetrexed	Docetaxel	
N	■	■	158	144	
Number of events, n (%)	■ (■%)	■ (■%)		-	
Median, months, (95% CI)	15.8 (10.3, -)	8.2 (5.9, 10.9)	9.0 (7.6, 9.6)	9.2 (7.5, 11.3)	
HR (95% CI)	0.49 (0.32, 0.75)		0.92 (0.69, 1.22)		0.53 (0.32, 0.89)

^a Adenocarcinoma only non-squamous patients

^b Retrospective analysis of adenocarcinoma patients from Hanna (2004)

- = not reached; CI = confidence interval; HR = hazard ratio; PD-L1 = programmed death ligand 1.

Source: Table B.6-51, and Figures B.6.25-26, p164 and Table C.2-10, Section C of the Pembrolizumab submission; and Scagliotti et al. (2009)

- 6.29 In PD-L1 TPS $\geq 50\%$ patients, there was a statistically significant gain in OS associated with pembrolizumab over pemetrexed (HR = 0.53; 95% CI 0.32, 0.89). The approach of excluding large cell patients favours pembrolizumab (pemetrexed vs docetaxel - large cell analysis: HR = ■, 95% CI ■, ■; adenocarcinoma analysis: HR = ■; 95% CI ■, ■). Interpretation of the results of the indirect comparison should consider the imbalances in disease characteristics for the common reference docetaxel treatment arm across the Scagliotti vs KN-010 datasets for ECOG PS of 0 (■% vs ■%) and disease stage IV (■% vs ■%).
- 6.30 Results for all indirect comparisons are tentative due to transitivity issues across the KN-010 and Scagliotti datasets in terms of time of trial conduct, PD-L1 positivity (the prognostic impact of which remains inconclusive) and other baseline prognostic characteristics, and the exploratory nature of the analyses.
- 6.31 The PSCR (p4) argued that PD-L1 expression levels do not have a prognostic role and that the differences observed in baseline characteristics across the studies used in the indirect comparison “balance out” overall. The ESCs considered that this did not address the issue of transitivity across the KN-010 trial and Scagliotti et al 2009 dataset.
- 6.32 The ESCs also considered that the methodological issues in the indirect comparison of pembrolizumab with pemetrexed limited the validity of the results. The ESCs were concerned that the pemetrexed trials did not enrol patients on the basis of PD-L1 expression, that there was up to a 10-year time difference between the pemetrexed and pembrolizumab trials, and that the trials differed in the dose of the common reference used (docetaxel: 75 mg/m² in KN-010 versus 500 mg/m² in Scagliotti et al 2009), baseline patient and disease characteristics, and stratification of subgroups. The ESCs also noted that Scagliotti et al 2009 was a retrospective analysis and limited data were available about subsequent treatments.

Indirect comparison between pembrolizumab and nivolumab

- 6.33 The submission also presented an indirect comparison between pembrolizumab and nivolumab in NSCLC patients, with docetaxel as the common comparator. The data sources for nivolumab in squamous and non-squamous NSCLC populations were individual trials (CA-017 and CA-057, respectively) whilst histology data for pembrolizumab were non-prespecified subgroups from Trial KN-010. There was also no stratification at randomisation by histology subtype in Trial KN-010.
- 6.34 The indirect comparison between pembrolizumab treated patients who had PD-L1 $\geq 50\%$ versus all nivolumab treated patients (unselected by PD-L1 status) favours pembrolizumab if PD-L1 expression is also a treatment effect modifier for nivolumab (HR = ■■■; 95% CI ■■■, ■■■). The indirect comparison between pembrolizumab and nivolumab in patients who had PD-L1 $\geq 1\%$ indicated no statistically significant gain in OS between both PD-1 inhibitors (HR = ■■■; 95% CI ■■■, ■■■).

Comparative harms and extended assessment of comparative harms

Direct comparison of safety between pembrolizumab and docetaxel

- 6.35 Table 11 summarises AEs of special interest (AEOSI) from the TPS $\geq 50\%$ subgroup of the KN-010 trial.

Table 11: KN-010: AEOSIs[∞] and pneumonitis: Pembrolizumab treatment groups pooled, APaT population (TPS ≥50%, data cut-off: 30 September 2015)

Subjects in population (AEOSI)	Docetaxel 75 mg/m ² Q3W N=133	Pembrolizumab pooled (2 mg/kg and 10 mg/kg doses) N=288	Risk difference % (RD) (95% CI) Pembrolizumab minus docetaxel	Relative risk (RR) (95% CI) Pembrolizumab minus docetaxel
	n (%)	n (%)		
With one or more AEs	9 (6.8)	66 (22.9)	16.1% (9.7%, 22.6%)	3.4 (2.0, 8.4)
With drug-related† AEs	4 (3.0)	55(19.1)	16.1% (10.7%, 21.4%)	6.4 (2.4, 17.2)
With toxicity grade 3-5 drug-related AEs	2 (1.5)	14 (4.9)	3.4% (0.1%, 6.6%)	3.2 (0.7, 14.0)
With serious drug-related AEs	2 (1.5)	17 (5.9)	4.4% (1.0%, 7.8%)	3.9 (0.9, 16.7)
Who died due to a drug-related AE	1 (0.8)	2 (0.7)	-0.1% (-1.8%, 1.7%)	0.9 (0.1, 10.1)
Discontinued due to a drug-related AE	2 (1.5)	9 (3.1)	1.6% (-1.2%, 4.5%)	2.1 (0.5, 9.6)
Discontinued due to a serious drug-related AE	2 (1.5)	5 (1.7)	0.2% (-2.3%, 2.8%)	1.2 (0.2, 5.9)
With Grade ≥ 2 pneumonitis with a potential immunologic etiology	2 (1.5)	15 (5.2)	3.7% (-0.4%, 7.0%)	3.5 (0.8, 14.9)

[∞] Safety parameters for AEOSIs that were identified a priori constituted "Tier 1" safety endpoints. Other safety parameters were considered Tier 2 or Tier 3. Membership in Tier 2 required that at least 4 subjects in any treatment group exhibited the event; all other AEs and predefined limits of change belonged to Tier 3

Risk difference and relative risks calculated during the evaluation using Stata Version 14.1.

Bolded results are statistically significant.

† Determined by the investigator to be related to the drug.

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.

AE = adverse event; APaT = all patients as treated; AEOSI = adverse events of special interest; CI = confidence interval; Q3W = every three weeks; TPS = tumour proportional score.

Source: Modified from Table B.6.23, p142 of the main submission

- 6.36 Safety data in the PD-L1 ≥50% subgroup were similar to those of the ITT population (all positive, TPS ≥1%). There were significantly higher drug-related, Grade 3-5 drug-related, and serious drug-related AEOSI in the pooled pembrolizumab group compared to the docetaxel group. There was a higher, but non-statistically significant, proportion of subjects in the pooled pembrolizumab treatment arms with Grade ≥2 pneumonitis (with a potential immunologic etiology) compared to docetaxel (5% vs 1.5%). These data relate to the pooled pembrolizumab 2 mg/kg and 10 mg/kg doses rather than to the pembrolizumab 2 mg/kg dose alone; the number of events were small in the latter.
- 6.37 Table 12 summarises analyses of Tier 2 AEs (at least 4 subjects in any treatment group) from the KN-010 trial.

Table 12: KN-010: Analysis of Tier-2[∞] adverse events, APaT Population (TPS ≥50%)

Treatment arm	n (%)	Difference in % vs Docetaxel 75 mg/m ² Q3W	Difference in % vs Pembrolizumab 2 mg/kg Q3W
		Estimate (95% CI) [†]	Estimate (95% CI) [†]
Subjects in population			
Docetaxel 75 mg/m ² , Q3W	133		
Pembrolizumab 2 mg/kg, Q3W	137		
Pembrolizumab 10 mg/kg Q3W	151		
With drug-related[‡] AEs			
Docetaxel 75 mg/ m ² Q3W	105 (78.9)		
Pembrolizumab 2 mg/kg, Q3W	93 (67.9)	-11.1 (-21.4, -0.5)	
Pembrolizumab 10 mg/kg Q3W	109 (72.2)	-6.8 (-16.6, 3.4)	4.3 (-6.3, 14.9)
With serious drug-related AEs			
Docetaxel 75 mg/ m ² Q3W	21(15.8)		
Pembrolizumab 2 mg/kg Q3W	12 (8.8)	-7.0 (-15.2, 0.8)	
Pembrolizumab 10 mg/kg Q3W	18 (11.9)	-3.9 (-12.3, 4.2)	3.2 (-4.1, 10.4)
Discontinued due to a drug-related AE			
Docetaxel 75 mg/ m ² Q3W	12 (9.0)		
Pembrolizumab 2 mg/kg Q3W	9 (6.6)	-2.5 (-9.4, 4.2)	
Pembrolizumab 10 mg/kg Q3W	8 (5.3)	-3.7 (-10.4, 2.4)	-1.3 (-7.4, 4.5)
With dose modification due to AE			
Docetaxel 75 mg/ m ² Q3W	54 (40.6)		
Pembrolizumab 2 mg/kg Q3W	51 (37.2)	-3.4 (-14.9, 8.2)	
Pembrolizumab 10 mg/kg Q3W	53 (35.1)	-5.5 (-16.7, 5.8)	-2.1 (-13.2, 8.9)
With any Grade 3-5 AE			
Docetaxel 75 mg/ m ² Q3W	75 (56.4)		
Pembrolizumab 2 mg/kg, Q3W	69 (50.4)	-6.0 (-17.8, 5.9)	
Pembrolizumab 10 mg/kg Q3W	76 (50.3)	-6.1 (-17.5, 5.6)	-0.0 (-11.5, 11.5)
With any drug-related Grade 3- 5 AE			
Docetaxel 75 mg/ m ² Q3W	45 (33.8)		
Pembrolizumab 2 mg/kg Q3W	18 (13.1)	-20.7 (-30.5, -10.8)	
Pembrolizumab 10 mg/kg Q3W	33 (21.9)	-12.0 (-22.4, -1.6)	8.7 (-0.1, 17.5)

[∞] Safety parameters for AEOSIs that were identified a priori constituted "Tier 1" safety endpoints. Other safety parameters were considered Tier 2 or Tier 3. Membership in Tier 2 required that at least 4 subjects in any treatment group exhibited the event; all other AEs and predefined limits of change belonged to Tier 3

[‡] Determined by the investigator to be related to the drug.

Every subject is counted a single time for each applicable specific adverse event category.

MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug are excluded. AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment

AE = adverse event; AEOSI = adverse events of special interest; APaT = all patients as treated; CI = confidence interval; Q3W = every three weeks; TPS = tumour proportional score

Source: Table B.6.16, p132 of the submission

- 6.38 There were less drug-related, serious drug-related, AE related discontinuations and dose modifications in the pembrolizumab arm versus docetaxel, although these differences were not statistically significant. However, there was an approximate 20% and 12% lower proportion of any drug-related Grade 3-5 AEs in the pembrolizumab 2 mg/kg and 10 mg/kg treatment arms, respectively, compared to the docetaxel arm. These differences were statistically significant. The extent of any drug-related Grade

3-5 adverse events appeared less in the lower pembrolizumab 2 mg/kg dose compared to the higher 10 mg/kg dose although the risk difference was not statistically significant (difference in %: 8.7%; 95% CI –0.1%, 17.5%).

- 6.39 There was an increased risk of immune-related AEs associated with pembrolizumab. Safety data from the KN-010 trial indicated these events were rare, although the risk may be increased in clinical practice compared to an experimental setting where there was likely to be a heightened awareness and recognition of immune-related AEs, and likely early intervention before such events progressed to a more severe grade.
- 6.40 The PSCR (p5) stated that immune-related adverse events should be considered in the context of the overall safety profile, and that, if AEs could be greater in practice than in clinical trials, this would apply equally to pembrolizumab as it would docetaxel. The ESCs noted that pembrolizumab was associated with increased immune adverse events compared to docetaxel and that this was of clinical significance.
- 6.41 The submission provided some additional information from a Periodic Safety Update Report (PSUR). The PSUR covered a period from 4 September 2015 to 3 March 2016 during which there have been no regulatory or manufacturer actions resulting in marketing authorisation withdrawal or suspension, failure to obtain marketing authorisation renewal, restriction on distribution, clinical trial suspension, dosage modification, change in target population, or pharmaceutical changes for safety reasons.

Indirect comparison of safety between pembrolizumab and pemetrexed

- 6.42 Table 13 summarises safety data across the KN-010 and Scagliotti datasets.

Table 13: A comparison of toxicities across Scagliotti (Hanna 2004 trial) and KN-010 (total trial population, pembrolizumab 2 mg/kg dose, all cause AEs ≥ Grade 3

≥ Grade3 AE	Hanna et al 2004		KN-010	
	% Pemetrexed patients (N=265)	% Docetaxel patients (N=276)	% Docetaxel Patients (N=133)	% Pembrolizumab 2 mg/kg Patients (N=137)
Neutropaenia	5.3	40.2	13.4	█
Febrile neutropaenia	1.9	12.7	5.3	██

AE = adverse event

Source: Hanna et al. (2004)

- 6.43 No formal statistical comparisons were presented. The submission noted that there was an inadequate match between the KN-010 and Scagliotti safety data and that it was uncertain whether AE data for pemetrexed were all-cause or treatment-related. The data presented have limited usefulness for informing the comparative safety of pembrolizumab with pemetrexed. This argument is reasonable. The rate of neutropenia and febrile neutropenia in the docetaxel arm varied across the KN-010 and Hanna trials indicating poor exchangeability for any indirect comparison of this AE. The majority of other ≥ Grade 3 AEs were rare. Statistical analyses of these events are unlikely to be informative. The submission stated that a naïve comparison

of the rates of adverse events suggests that pembrolizumab and pemetrexed have “different but comparable” safety profiles.

- 6.44 The PBAC considered that pembrolizumab was overall better tolerated than its main comparators, despite the increased risk of immune-related adverse events.

Benefits/harms

- 6.45 **Direct comparison with docetaxel (KN-010 trial):** A summary of the comparative benefits and harms for the likely recommended dose of pembrolizumab (2 mg/kg) versus docetaxel, in the squamous NSCLC population who have evidence of a high level of PD-L1 expression (TPS $\geq 50\%$), is presented in Table 14.

Table 14: KN-010: Comparative benefits and harms for pembrolizumab 2 mg/kg Q3W vs docetaxel (PD-L1 $\geq 50\%$)

	Pembro	Doc	Absolute difference		HR (95% CI)
Benefits^a					
Median OS, months (95% CI)	N=139 15.8 (11.0, 26.0)	N=151 8.2 (6.6, 10.4)	7.6		0.54 (0.39, 0.73)
Harms					
	Pembro	Doc	Event rate/100 patients		RD (95% CI)
			Pembro	Doc	
Subjects with Grade ≥ 2 pneumonitis with a potential immunologic etiology	15/288 ^b	2/133	5.2	1.5	3.7% (-0.4%, 7.0%)
Patients with any drug-related Grade 3-5 AE	18/137	45/133	13.1	33.8	-20.7 (-30.5, -10.8)

^a Updated database cut-off: 31 March 2016 with extended median follow-up.

^b Results for both strengths of pembrolizumab.

AE = adverse event; HR = hazard ratio; RD = risk difference; Pembro = pembrolizumab; Doc = docetaxel; CI = confidence interval; PD-L1 = programmed death ligand-1.

Source: Compiled from effectiveness and safety data presented in the submission and PSCR

- 6.46 Results were similar in the PD-L1 TPS $\geq 1\%$ squamous NSCLC population. A comparative benefit versus docetaxel was also presented for non-squamous NSCLC as the data indicated clinical heterogeneity across squamous and non-squamous histology subtypes and the indirect benefit compared with the main comparator of pemetrexed is unreliable.
- 6.47 On the basis of the direct evidence presented in the submission, in NSCLC patients with evidence of a high PD-L1 expression TPS $\geq 50\%$ and treated with pembrolizumab instead of with docetaxel:
- There was an increase in median overall survival by 8 months to 16 months and a corresponding reduction in the risk of death by almost 50%
 - For every 100 patients, 21 fewer patients would experience a drug-related Grade 3 -5 AE, but an additional 4 patients may experience \geq Grade 2 pneumonitis. These differences would be expected to be fairly similar between squamous and non-squamous histology subtypes.
- 6.48 **Indirect comparison with pemetrexed (KN-010 vs Scagliotti):** A summary of the indirect comparative benefits and harms for the likely recommended dose of

pembrolizumab 2 mg/kg (PD-L1 TPS $\geq 50\%$) versus pemetrexed (unselected by PD-L1 status) in the non-squamous NSCLC population is presented in the table below.

Table 15: Indirect comparison of benefits and harms for pembrolizumab 2 mg/kg Q3W (PD-L1 $\geq 50\%$ from KN-010) vs pemetrexed (unselected for PD-L1 from Scagliotti 2009) – All non-squamous NSCLC

	Pembro	Pemetrexed	Absolute difference	HR (95% CI)
Benefits				
Median OS, months (95% CI)	N=110 15.8 (10.4, -)	N=126 9.3 (7.8, 9.7)	6.5	0.60 (0.37, 0.97)
Harms				
The submission concluded that the safety profiles of pembrolizumab and pemetrexed were comparable (no meaningful statistical analyses of safety could be conducted).				

Median follow-up for KN-010 was 11 months (for the published database cut-off of 30 September 2015) and for Hanna was 7.5 months

- = median not reached; HR = hazard ratio; Pembro = pembrolizumab; CI = confidence interval; PD-L1 = programmed death ligand-1

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

- 6.49 On the basis of the indirect evidence presented in the submission, in NSCLC patients of non-squamous histology subtype:
- Patients with evidence of a high PD-L1 expression (TPS $\geq 50\%$) and who are treated with pembrolizumab will experience a 40% reduced risk of death compared to patients with unknown PD-L1 status and treated with pemetrexed.
 - Safety is expected to be fairly similar between the two treatments.
- The ESCs considered that, due to the methodological issues in the indirect comparison, these results could not be interpreted with confidence.

Clinical claim

- 6.50 **Squamous NSCLC with TPS $\geq 50\%$ PD-L1:** The submission described pembrolizumab as superior in terms of comparative effectiveness and superior in terms of comparative safety over docetaxel. This claim was not adequately supported:
- The effectiveness results for the small squamous subgroup were inconclusive. The submission's approach to include non-squamous data conflicted with evidence suggesting clinical heterogeneity in the OS results across these histology subgroups. A further justification provided in the submission for effectiveness in the squamous NSCLC was that "It is worthwhile noting that a study with another PD-L1 inhibitor, nivolumab, did demonstrate an overall survival benefit in a population with NSCLC of squamous histology...and an indirect comparison of nivolumab and pembrolizumab found that these drugs are non-inferior in terms of efficacy".
 - For safety, pembrolizumab appeared to be superior in terms of \geq Grade 3 AEs and specifically hematologic AEs associated with docetaxel. However one would expect immune-related AEs to be higher in clinical practice than what was observed in a trial setting.
- 6.51 The PSCR (p4) claimed that the totality of evidence with PD-1 inhibitors (such as nivolumab) supported a clinical benefit compared to docetaxel in squamous patients. The ESCs considered that this claim of class effect was not supported by adequate clinical evidence.

- 6.52 **Non-squamous NSCLC with TPS \geq 50% PD-L1:** The submission described pembrolizumab as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over pemetrexed. This claim was not adequately supported. The evidence was based on an indirect comparison with transitivity and methodological issues. The safety profiles appear different although direct data are required to be conclusive.
- 6.53 The PBAC considered that the claim of superior comparative effectiveness of pembrolizumab over docetaxel and pemetrexed was reasonable, but noted that the claim of superior comparative effectiveness of pembrolizumab over pemetrexed also relied on accepting the superior effectiveness of pembrolizumab in the TPS \geq 50% subgroup over the full ITT population in the pembrolizumab trial. The PBAC also considered that the effectiveness of pembrolizumab was likely to be:
- similar for squamous and non-squamous NSCLC
 - improved in patients with greater levels of PD-L1 expression tested before the start of pembrolizumab therapy, if the variation in treatment effect suggested in the trial can be applied to the Australian context.
- 6.54 The PBAC considered that the claim of superior comparative safety of pembrolizumab over docetaxel and non-inferior comparative safety of pembrolizumab over pemetrexed was reasonable.

Claim of co-dependence

- 6.55 The submission presented a claim that treatment guided by PD-L1 status, where PD-L1 strong positives (i.e. TPS \geq 50%) are treated with pembrolizumab, and PD-L1 negatives (i.e. TPS $<$ 1%) and weakly positives (i.e. TPS 1–49%) are treated with docetaxel or pemetrexed, results in improved outcomes versus the comparator, which is no testing and docetaxel or pemetrexed treatment. This was based on the conclusion that the test is accurate, that there is no prognostic impact of PD-L1 status (therefore patients with TPS \geq 50% in the trial treated with docetaxel can reasonably approximate an unselected population treated with docetaxel), that pembrolizumab has improved effectiveness and improved or non-inferior safety, when compared to docetaxel or pemetrexed treatment and that there is a treatment effect modification by PD-L1 status. The PBAC noted other important unresolved issues regarding PD-L1 testing, the optimal threshold for PD-L1 positivity, the predictive effect of PD-L1 expression, the extent of incremental effectiveness of pembrolizumab over its comparators, and consequential uncertainties in the economic evaluation of the co-dependent technology. The PBAC noted that some of these issues were relevant to MSAC, and so awaited MSAC's assessment before drawing any conclusions.
- 6.56 The evidence provided suggested that Asian patients with PD-L1-positive NSCLC had a worse prognosis than those who had PD-L1-negative tumours. However, the evidence, which also indicated an improved prognosis in Caucasian patients, is inconclusive due to the limited number of studies and the many inconsistencies between them. Thus, further evidence is required to determine if there is a true prognostic effect of PD-L1 in Caucasian patients, and at what stage of disease.

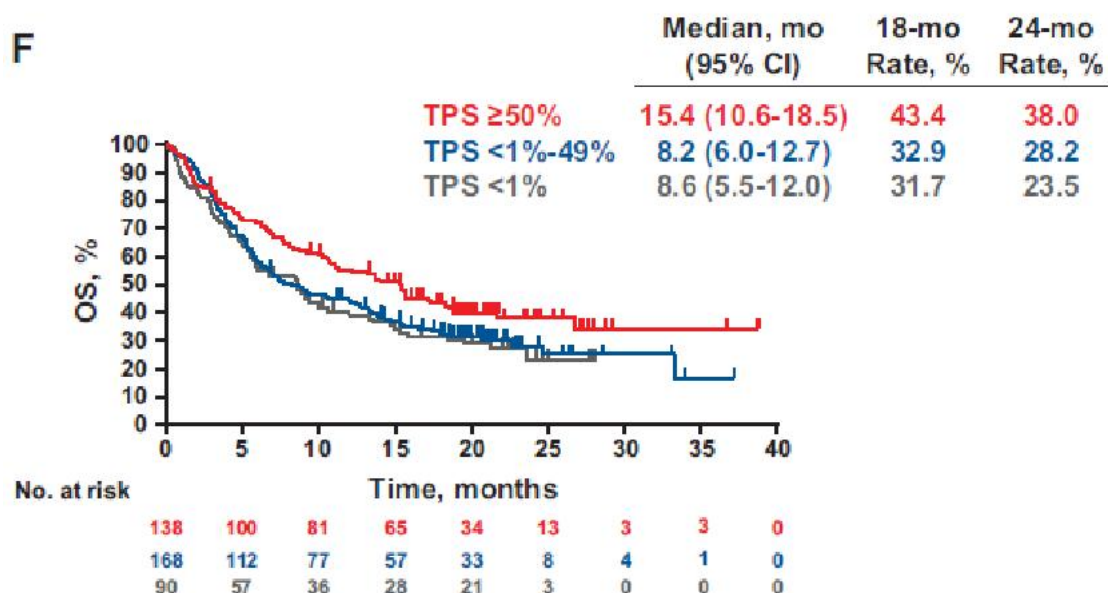
6.57 In patients with squamous histology, treatment effectiveness of pembrolizumab compared to docetaxel was inconclusive. In patients with non-squamous histology, while pembrolizumab was associated with significantly improved benefit compared to docetaxel, evidence presented for the main comparison, pembrolizumab versus pemetrexed, was based on an indirect comparison and was problematic. Evidence to support the treatment effect modification by PD-L1 status was limited to a comparison of strongly positive (TPS $\geq 50\%$) vs weakly positive (TPS 1–49%).

Further evidence beyond Trial KN-010 of treatment effect variation

6.58 Study KN-001 was a Phase 1 single-arm study which showed that there was increasing OS associated with pembrolizumab as PD-L1 TPS increased (from $<1\%$ [median OS = 8.6 months; 18-month OS rate of 32%], 1%–49% [median OS = 8.2 months; 18-month OS rate of 33%] and $\geq 50\%$ [median OS = 15.4 months; 18-month OS rate of 43%]).

6.59 The ESCs noted the paucity of evidence to support the prior claim of codependence between being PD-L1 positive or not (Figure 4). These results came from one single-arm study (KN-001), with a sample of only 90 patients with TPS $<1\%$.

Figure 4: (KN-001): Kaplan Meier curves of overall survival in previously treated NSCLC patients by PD-L1 expression levels TPS $\geq 50\%$, 1%-49%^β, and $<1\%$



^β The title of the figure in the abstract by Hui et al indicated the middle PD-L1 stratum was 1–49% rather than $<1\%$ -49%. The former appeared more plausible and informative for mutually exclusive subsets.

CI = confidence interval; PD-L1 = programmed death ligand 1; TPS = tumour proportion score.

Source: Figure 2, Panel B from Hui et al (2016)^c.

^c Abstract presentation by Hui et al. Long-Term Overall Survival For Patients With Advanced NSCLC Enrolled In the KEYNOTE-001 Study of Pembrolizumab. American Society of Clinical Oncology (ASCO) Annual Meeting June 3-7, 2016, Chicago, Illinois.

- 6.60 Evidence of a treatment effect variation of anti-PD1 agents in NSCLC, by PD-L1 expression status, was also published in a recent meta-analysis by Abdel-Rahman et al (2016)^d. The meta-analysis assessed the correlation between PD-L1 levels and effectiveness outcomes of PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, atezolizumab, durvalumab and avelumab) in advanced NSCLC. The benefit from PD-1 inhibitors versus docetaxel in second-line treatment of NSCLC appeared to be limited to the PD-L1 >1% population.
- 6.61 The submission presented data in the translation section for nivolumab, by PD-L1 expression, in patients with non-squamous (CheckMate 057 trial) and squamous (CheckMate 017 trial) histology. These trials have been previously considered by the PBAC (nivolumab for non-squamous and squamous NSCLC, March 2016 PSDs). The data presented supported the conclusion of treatment effect modification by PD-L1 status in patients with non-squamous histology, but not in patients with squamous histology. The submission raised several issues with the CheckMate 017 data:
- the biological plausibility of a treatment effect variation is equally applicable in squamous as it is in non-squamous (as it relates to the biological effect that the PD-1 antibody has on the ability of the tumour to evade the immune system);
 - a trend, although not significant, was suggestive of a treatment effect variation by PD-L1 expression;
 - a substantial proportion of patients (17%) had unquantifiable PD-L1 expression and these patients showed the biggest difference favouring nivolumab; and
 - higher PD-L1 expression thresholds were associated with fewer patient numbers.
- 6.62 The literature has reported inconsistencies in the treatment effect variation of PD-L1 expression on the effectiveness of PD-1 /PD-L1 inhibitors, across squamous and non-squamous histology subtypes. A meta-analysis by Gandini et al (2016)^e showed that PD-L1 expression correlated with the clinical response to antibodies targeting the PD-1/PD-L1 axis in non-squamous NSCLC and not in squamous NSCLC (odds ratio (OR) of summary objective response rate for PD-L1 positive vs negative: squamous NSCLC: OR = 1.49; 95% CI 0.48, 4.64; non-squamous NSCLC: OR = 3.78; 95% CI 1.54, 9.24).
- 6.63 Nivolumab data in squamous NSCLC from CheckMate-017 (Brahmer (2015)) indicated the benefit of nivolumab over docetaxel was independent from PD-L1 expression regardless of the threshold used. In contrast, there was a convincing treatment effect variation with PD-L1 expression in the nivolumab versus docetaxel non-squamous trial (CheckMate-057, Borghaei (2015) and Horn (2015)). Overall, there are inadequate robust data currently available to support a confident position in this regard.

Economic analysis

^d Abdel-Rahman O. Correlation between PD-L1 expression and outcome of NSCLC patients treated with anti-PD-1/PD-L1 agents: A meta-analysis. *Critical reviews in oncology/hematology*. 2016;101:75-85

^e Massi D, Mandalà M. PD-L1 expression in cancer patients receiving anti PD-1/PD-L1 antibodies: A systematic review and meta-analysis *Critical reviews in oncology/hematology*. 2016; 100: 88-98.

- 6.64 A modelled economic evaluation, cost-utility analysis (CUA) and cost-effectiveness analysis (CEA) (life-years gained), was presented based on the claims of:
- superior effectiveness and safety of pembrolizumab compared to docetaxel in patients with squamous NSCLC who strongly express PD-L1 (TPS \geq 50%); and
 - superior effectiveness and non-inferior safety of pembrolizumab compared to pemetrexed in patients with non-squamous histology who strongly express PD-L1 (TPS \geq 50%).
- The submission presented an ICER of \$45,000 - \$75,000 per quality-adjusted life year (QALY) based on OS and PFS data from the KN-010 trial and the HR from an indirect comparison using KN-010 and Scagliotti et al (2009), extrapolated to 7 years (from a median follow-up of 13.1 months in KN-010) and applying utility weights from the KN-010 trial.
- 6.65 The evidence presented in the submission did not support these claims. The submission's claim of superiority in patients with squamous histology was generalised based on the whole TPS \geq 50% population of KN-010. This was not appropriate. In patients with squamous histology, no significant difference in OS or PFS was observed. In patients with non-squamous histology, the claim was based on the results from an indirect comparison of datasets sourced from different settings and populations which were unlikely to be sufficiently exchangeable to enable a meaningful comparison of outcomes.
- 6.66 The ESCs agreed with the commentary that the clinical claims made in the submission, which were used as the basis for economic modelling, were not substantiated by the clinical evidence presented in the submission. Therefore the ESCs were concerned that the overarching issues in the economic analysis were grounded in issues with the clinical evidence presented in the submission.
- 6.67 Translation issues identified by the submission are presented in Table 16.

Table 16: Key structural features of the model

Issue	Results
Applicability premodelling studies	
Applicability of trials	The submission concluded that there were no significant differences between patients enrolled in the trials (KN-010 and Scagliotti et al 2009) and those eligible for pembrolizumab (based on patients enrolled in the PIVOTAL study). The subgroups selected by the submission to be modelled (i.e. TPS \geq 50% ITT for the squamous subset and the adenocarcinoma subgroup for the non-squamous subset) did not match the proposed populations; this approach favoured pembrolizumab and the results may not be applicable. The ESCs considered that the use of the ITT data for modelling of the squamous subgroup and the adenocarcinoma subgroup data for modelling of the non-squamous subgroup compromised the validity of the modelled results.
Prognostic effect of PD-L1	The submission did not identify a clear prognostic effect of PD-L1 status in the literature. This may be reasonable, however absence of evidence for a prognostic effect is not evidence of no effect, and this remains an issue of uncertainty.
Prevalence of PD-L1 positivity	Prevalence in Australian patients screened for KN-001 and KN-010 were used in the economic model. This may be reasonable if the same antibody clone for testing that was used in the KN-010 and KN-001 trials is used in clinical practice. However, caution is required when extrapolating the benefit observed in TPS \geq 50% patients from the KN-010 trial to TPS \geq 50% patients identified using different PD-1/PD-L1 antibody clones that may be used across different pathology laboratories in practice. The Dako assay used in the nivolumab trials does

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	<p>appear to be reasonably concordant with the assay used in the pembrolizumab trials. Varying the estimate of prevalence did not substantively affect the economic analysis, but did affect the financial estimates.</p> <p>The PSCR (p2) stated that the 22C3 antibody concentrate has been made available to enable the development of laboratory developed tests, regardless of platform.</p> <p>The ESCs and the PBAC noted the letter of 5 September 2016 from the RCPA, which stated that antibody testing for PD-L1 positivity was associated with issues of reproducibility, robustness and equivalence of results across different assays. The RCPA also stated that PD-L1 expression had been shown to be inducible and dynamic, which would make identifying patients likely to benefit from PD-L1 agents a challenging issue.</p>
Effect of the timing of the sample tested (archival or fresh)	<p>Results for OS and PFS were compared between patients who were tested on archival (i.e. treatment-naïve) or fresh (i.e. treatment-experienced) samples. The submission concluded that both subgroups of patients would gain similar benefit from pembrolizumab and that patients would not need to have additional biopsy material taken for testing of PD-L1 expression. However the submission did not consider that patients could receive more than one PD-L1 test – at diagnosis of advanced disease, and on additional re-biopsied material, if taken, after treatment with TKIs or platinum-based chemotherapy.</p> <p>The ESCs considered that both re-testing of archival biopsy samples and re-biopsy may be necessary. Furthermore, the ESCs were concerned that PD-L1 expression may not be stable over time and may vary following different lines of therapy.</p>
Effect of pembrolizumab by histology	<p>The submission concluded that histology did not impact the efficacy of pembrolizumab or docetaxel or the safety of pembrolizumab. However, pemetrexed has been shown to interact with histology. For squamous patients, the results of the KN-010 trial for the subgroup who strongly express PD-L1 (TPS $\geq 50\%$) regardless of histology were used in the economic model. The PSCR (p6) argued that, when the data for the squamous subgroup only was used in the model, the ICER remained under \$75,000, which the PSCR argued was cost-effective for an oncology treatment. Patients with squamous histology made up fewer than 20% of the TPS $\geq 50\%$ population. There was no conclusive evidence of survival benefit associated with pembrolizumab over docetaxel in the squamous subgroup, while a significant survival benefit was observed in the non-squamous subgroup. Tests for interaction conducted during the evaluation in the population who strongly express PD-L1 (TPS $\geq 50\%$) suggested a trend that patients with non-squamous histology may perform twice as well on pembrolizumab than those with squamous histology (as indicated by the ratio of hazard ratios), however this was not statistically significant. The statistical power of these analyses was limited by the small size of the squamous subgroup. This led to a bias in favour of pembrolizumab.</p> <p>The ESCs considered that the submission's argument that histology did not impact the efficacy or safety of pembrolizumab was not adequately supported by the clinical evidence. The PBAC considered that pembrolizumab may have a similar effect on squamous and non-squamous NSCLC.</p>
Indirect treatment comparison based on adenocarcinoma or non-squamous	<p>The submission identified heterogeneity in the composition of the non-squamous subgroups of KN-010 and Scagliotti et al (2009) and so the HR derived from an indirect comparison used in the base case analysis for pembrolizumab versus pemetrexed was based on the adenocarcinoma subset of the non-squamous subgroups of these trials. This was not a reasonable approach; the choice of the adenocarcinoma subset of the total non-squamous population for an indirect comparison favours pembrolizumab and does not mitigate the transitivity concerns with the trials.</p> <p>The ESCs agreed with the commentary that selecting the adenocarcinoma subset of the non-squamous subgroup to inform the indirect comparison of pembrolizumab versus pemetrexed was methodologically incorrect and that it did not address issues with transitivity. The ESCs were concerned that the transitivity issues in the indirect comparison of pembrolizumab and pemetrexed did not allow for a robust economic analysis.</p>
PD-L1 status as treatment effect modifier	<p>A PD-L1 TPS threshold of 50% was claimed to be a treatment effect modifier based on the plausibility of treatment effect variation, prespecification of this analysis, and statistical analysis of the ratio of HRs across subgroups categorised as TPS $\geq 50\%$ vs TPS 1–49%. While it may be reasonable to model PD-L1 testing and pembrolizumab treatment in the non-</p>

	<p>squamous subgroup, if the evidence to support either PD-L1 testing and/or pembrolizumab treatment in the squamous subgroup is inadequate, then the modelled results may not be a robust estimate for the squamous subgroup.</p> <p>The PSCR (p4) argued that the KN-010 trial was not sufficiently powered to detect treatment effect variation by PD-L1 status within the squamous subgroup.</p> <p>The ESCs considered that there was insufficient evidence regarding PD-L1 status as a treatment effect modifier in the squamous subgroup.</p>
Extrapolation premodelling studies	
Extrapolation of PFS and OS	<p>Kaplan-Meier OS and PFS curves from KN-010 were used in the model up to 52 and 28 weeks respectively for OS and PFS. Data was modelled separately by treatment and by histology. Parametric models were fitted to the remaining Kaplan-Meier data, and model selection was based on an assessment of AIC and BIC, and clinical plausibility of results. Extrapolation may be sensitive to the point at which the parametric model takes over from the Kaplan-Meier data and therefore a clear rationale for the selection of the time point is required. The impact of fitting and extrapolation for different time points and for all trial data, were not tested as part of sensitivity analyses in the submission. The model structure did allow for the selected time point to change from 28 weeks to 9 weeks for PFS, however, no alternative data truncation time points were allowed for OS. Therefore uncertainty remains in both model selection and the modelled estimates.</p> <p>The PSCR (p5) stated that, when the full parametric exponential models are selected (base-case model), the ICER decreased by \$ [REDACTED] to \$45,000 - \$75,000.</p> <p>The ESCs considered that it was unclear whether the analysis presented in the PSCR fitted the parametric models to all data available (as requested in the suggestions for further interaction in the commentary), or whether the same model used in the base case analysis was used (and so only fitted to data available after week 52), but applied from time = 0.</p>
Time horizon	<p>A review of submissions for second-line NSCLC treatments to three HTA agencies demonstrated time horizons ranging from 2 to 15 years. A time horizon of seven years was used in the economic evaluation. The time horizon chosen was not consistent with previous submissions to the PBAC for advanced NSCLC (five years). The ICER was sensitive to such a change.</p> <p>The PSCR (p6) stated that the costs and benefits associated with immunotherapies such as pembrolizumab required a longer time horizon to be fully considered.</p> <p>The ESCs considered that a time horizon of five years would be more appropriate.</p> <p>The PBAC noted that the time horizon of seven years used by the submission favoured pembrolizumab, and that changing the time horizon to five years would increase the base case ICER.</p>
Transformation premodelling studies	
AEs in false positives	<p>AE rates between PD-L1-positive and -negative patients in KN-001 were compared, with tests for statistically significant differences undertaken. AE rates were assumed to be the same for true positives and false positives treated with. This appeared reasonable.</p>
Utilities	<p>Utilities from KN-010 mapped to Australian values for pembrolizumab and docetaxel were found to be comparable to utilities identified for NSCLC patients in the literature. Trial-based utilities mapped to Australian values by progression status were used in the economic model. Utility differences modelled were not observed to be statistically significant, and a higher utility for pembrolizumab was modelled in the progressive disease state. This might not be reasonable as this was based on data to approximately 30 days post-progression (of an average 10 months in the progressive disease health state). It was not reasonable to assume that a higher utility for pembrolizumab treatment continued after treatment has stopped without significant, ongoing data.</p> <p>The ESCs agreed with the commentary that it was not appropriate to assume that utilities at 30 days post-progression would remain constant throughout the duration of the post-progression disease state. The ESCs considered that patients were likely to experience worse utilities later in disease progression than at an earlier stage.</p> <p>Utilities for pemetrexed treatment were assumed to be the same as for docetaxel treatment.</p>

	<p>This was not appropriate given the different safety profiles of docetaxel and pemetrexed. This led to bias in favour of pembrolizumab.</p> <p>The ESCs considered that the utilities for pemetrexed treatment should not have been assumed to be the same as for docetaxel treatment.</p>
Resource utilisation for disease management	<p>The submission concluded that resource utilisation in PIVOTAL may overestimate resource utilisation for disease management, as the number of hospital outpatient visits may include chemotherapy administrations, which would be accounted elsewhere in the model. An alternative source was identified (NICE TA347). Resource utilisation for disease management was based on that reported in the NICE Technology Appraisal for nintedanib for later-line NSCLC. This was reasonably justified, however the cost of the additional GP consultation every 10 weeks may be inappropriate.</p>
Effect of PD-L1 testing on re-biopsy rates	<p>Pathologist members of the sponsor's Pathologist Advisory Board were surveyed. The majority of respondents (4/5) answered that re-biopsy rates would not change with the introduction of the PD-L1 test. The submission assumed the same re-biopsy rate across both arms of the economic model. This would be a reasonable conclusion if it could be assumed that PD-L1 expression status would not change with prior treatment, however there is some evidence to suggest that it may.</p> <p>The ESCs considered that, if PD-L1 testing was subsidised by the Medical Benefits Schedule, it would drive and potentially change clinical practice such that the rates of re-testing archival biopsies or re-biopsies would increase.</p>

AE = adverse event; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; ICER = incremental cost-effectiveness ratio; HR = hazard ratio; HTA = health technology assessment; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PD-L1 = programmed death-ligand 1; PFS = progression-free survival.

Source: Table C.5-1, pp304-310 of the submission

- 6.68 The submission did not adequately address the applicability issue regarding which PD-L1 test will be used in the Australian context, given the potential availability of several PD-1/PD-L1 assays. Accuracy and prevalence estimates used in the modelling may differ from Australian clinical practice depending on the assay(s) available.
- 6.69 The submission presented a two phase modelled economic evaluation for patients with Stage IIIB/IV NSCLC where PD-L1 status was determined in the 'Testing phase'; and treatment after disease progression from platinum-doublet chemotherapy was guided by PD-L1 status in the 'Treatment phase'. Each sub-cohort of patients (by PD-L1 status and treatment) entered a Markov model, where three health states were possible: progression-free; progressive disease; and dead. The modelled time horizon was seven years. The ESCs considered that the time horizon of seven years was optimistic and that five years would have been more appropriate, consistent with the recent PBAC advice in the context of nivolumab for the treatment of NSCLC. The PBAC agreed with the ESCs that a five-year time horizon would be more appropriate.
- 6.70 The comparator in the 'Testing phase' was no PD-L1 testing, while that in the 'Treatment phase' was determined by histology: docetaxel for patients with squamous histology, and pemetrexed for patients with non-squamous histology.
- 6.71 The key structural features of the model are presented in Table 17.

Table 17: Key structural features of the model

	Summary	Able to be varied?	Appropriate?
Duration	7 years	Yes	The ESCs considered that a 5-year time horizon would have been more appropriate, consistent with recent relevant advice by PBAC.
Cycle length	1 week	No	A one-week cycle length may be reasonable, however a three-week cycle would be more appropriate, as this is consistent with time between treatment administrations.
When tested	At diagnosis of advanced disease	No	Alternative scenarios for the timing of the test should also have been presented in scenario analyses.
Who tested	Stage IIIB/IV NSCLC	No	Evidence presented in the submission does support treatment effect modification by PD-L1 status in patients with non-squamous histology, however is inconclusive in patients with squamous histology.
Outcomes	QALYs, Lys	Can vary utility values	Yes
Methods used to generate results	Markov model. Cohort expected value analysis	No	Yes
Health states	Progression-free, progressive disease and dead	No	Yes
Transition probabilities	Based on PFS and OS from KN-010, or derived from application of HR from indirect comparison (for pemetrexed)	Yes.	It may also have been appropriate to present analyses for extrapolation based on model selection based on all reliable trial data available, rather than only that remaining after the time from which extrapolation takes over.

6.72 The model presented in the submission was structurally sound.

6.73 Variables used in the economic model are presented in Table 18.

Table 18: Variables in the economic model

Variable	Base case value	Source	Tested in sensitivity analyses?
Test cost	\$█	Based on MBS item █	No. Re-testing (4.8%) costs tested in evaluation sensitivity analyses
Re-biopsy	█% re-biopsy rate; assuming █% AEs	Re-biopsy rate: PIVOTAL study Re-biopsy AE: Heerink et al (2016)	Re-biopsy rate: Yes (█-█%) Re-biopsy AEs: No
Prevalence	█%	% Australian patients with TPS ≥50% PD-L1 expression screened for KN-010 and KN-001	Yes (█-█%)
Test performance	Sensitivity: █% Specificity: █%	CTA v GMP study (Appendix 20)	Yes, lower limit of 95% CI
Baseline risk by PD-L1 status	No difference	Systematic review	No
How costs and benefits of treatment have been accrued	Costs: one-off Benefits: over time	KN-010	Accrual of costs over time is tested in the evaluation.
Source of data, squamous population	Data included patients with squamous and non-squamous histology	KN-010 strong positive (TPS ≥50%), ITT population	KN-010 strong positive population (TPS ≥50%), squamous subgroup
Source of data, non-squamous population	Non-squamous data	KN-010 strong positive (TPS ≥50%), non-squamous subgroup	No
Treatment effect v docetaxel (in trial period)	Per trial	KN-010	No
Treatment effect v docetaxel (extrapolated)	Per trial, extrapolated treatment arms separately. OS curves do not converge within model time horizon	Section C.3.1 of the submission	Yes – different distributions tested
Treatment effect v pemetrexed	PFS: █ OS: █ Assumed for model time horizon	Indirect comparison, Section B.6.3 of the submission	Yes – different subgroup analysis of indirect comparison. 95% CIs are tested in the evaluation
Utilities: progression-free	Pembrolizumab: █ D/P: █	KN-010, mapped to Australian algorithm	Yes (by time-to-death)
Utilities: progressive-disease	Pembrolizumab: █ D/P: █	KN-010, mapped to Australian algorithm	Yes (by time-to-death)

Source: Compiled during the evaluation

6.74 The key drivers of the model are presented in Table 19.

Table 19: Key drivers of the model

Description	Method/Value	Impact
Pembrolizumab v pemetrexed OS HR	Derived from an indirect comparison of trials that have limited exchangeability.	High, favours PD-L1/pembrolizumab
Progression-free treatment costs	Applied a one-off truncated treatment cost, rather than cost per cycle for the proportion of patients in the progression-free health state.	High, favours PD-L1/pembrolizumab
Time horizon	7 years.	Moderate-high, favours PD-L1/pembrolizumab
Indirect comparison population	The HR for the indirect comparison was based on the adenocarcinoma subset of the non-squamous subgroups of trials that have limited exchangeability.	Moderate-high, favours PD-L1/pembrolizumab
Squamous OS and PFS data	KN-010 OS and PFS regardless of histology.	Moderate-high, favours PD-L1/pembrolizumab
Post progression treatment costs	Assumes higher post-progression treatment cost after comparator than pembrolizumab, due to higher comparator post-progression pemetrexed use.	Moderate, favours PD-L1/pembrolizumab

Source: Compiled during the evaluation

- 6.75 The results of the economic evaluation (with some re-specification) are presented in Table 20. The redacted table below shows ICERs in the range of \$45,000 - \$75,000 per QALY.

Table 20: Results of the economic evaluation

Component	PD-L1/pembrolizumab	SoC	Increment
Costs	\$██████	\$██████	\$██████
Lys	██████	██████	██████
QALYs	██████	██████	██████
Incremental cost/extra LY gained (with some re-specification)			\$██████
Incremental cost/extra QALY gained (with some re-specification)			\$██████

Source: Constructed during the evaluation from Section D Workbook (Pembrolizumab 2L NSCLC) v0607 FINAL.xlsm of the submission. The base case was re-specified to correct for i) the approach used to determine the proportion of patients who are true positives, false positives, true negatives and false negatives; and ii) drug acquisition costs to be based on the efficient combination of vials, allowable maximum PBS dose and update efficient funding of chemotherapy fees (1 July, 2016).

- 6.76 Additional scenarios of test/drug accessibility conducted during the evaluation (compared to standard of care) are presented in Table 21. The redacted table below shows ICERs ranging from \$45,000 - \$75,000 to \$105,000 - \$200,000 per QALY.

Table 21: Results of key scenario analyses conducted during the evaluation

	ICER vs SoC
Base case (with some re-specification) <ul style="list-style-type: none"> - MSAC funded test: testing at same time as EGFR, ALK - Strong positive patients (TPS ≥50%) eligible for pembrolizumab 	\$ [REDACTED] /QALY
No MSAC funded test <ul style="list-style-type: none"> - All patients eligible for pembrolizumab - Assumptions regarding treatment duration in PD-L1 negative (TPS <1%) and weak positives (TPS 1–49%) 	\$ [REDACTED] /QALY
MSAC funded test <ul style="list-style-type: none"> - All PD-L1 positive patients, defined as TPS ≥1%, eligible for pembrolizumab - Test performance for TPS ≥1% ([REDACTED]% sensitivity, [REDACTED]% specificity) - Assumptions regarding treatment duration in PD-L1 weak positives (TPS 1–49%) 	\$ [REDACTED] /QALY
MSAC funded test <ul style="list-style-type: none"> - Testing performed on sample taken after disease progression (i.e. treatment experienced) (100% re-biopsy rate) - Strong positive patients (TPS ≥50%) eligible for pembrolizumab - Assumes same prevalence (22.2%) 	\$ [REDACTED] /QALY
MSAC funded test: <ul style="list-style-type: none"> - Strong positive patients (TPS ≥50%) with squamous and non-squamous histology eligible for pembrolizumab, comparison to docetaxel (100% proportion squamous, implicitly assuming that the proportion of squamous in the KN-010 trial population (18.9%) is applicable to the Australian population) - Comparator docetaxel 	\$ [REDACTED] /QALY
MSAC funded test: <ul style="list-style-type: none"> - Strong positive patients (TPS ≥50%) with non-squamous histology only eligible for pembrolizumab (0% proportion squamous) - Comparator pemetrexed 	\$ [REDACTED] /QALY
MSAC funded test: <ul style="list-style-type: none"> - Strong positive patients (TPS ≥50%) with non-squamous histology only eligible for pembrolizumab (0% proportion squamous) - Comparator docetaxel 	\$ [REDACTED] /QALY
MSAC funded test: <ul style="list-style-type: none"> - Strong positive patients (TPS ≥50%) with squamous histology only eligible for pembrolizumab (100% proportion squamous and only patients with squamous histology) - Comparator docetaxel 	\$ [REDACTED] /QALY

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; MSAC = Medical Services Advisory Committee; SoC = standard of care

Source: Analyses conducted during the evaluation The base case was re-specified to correct for i) the approach used to determine the proportion of patients who are true positives, false positives, true negatives and false negatives; and ii) drug acquisition costs to be based on the efficient combination of vials, allowable maximum PBS dose and update efficient funding of chemotherapy fees (1 July, 2016).

Committee-In-Confidence information



End Committee-In-Confidence information

6.78 The results of key sensitivity analyses conducted during the evaluation are presented in Table 22. The redacted table below shows ICERs ranging from \$45,000 - \$75,000 to over \$200,000 per QALY.

Table 22: Results of key sensitivity analyses

Sensitivity analyses		Incremental		ICER	% change
		Costs	Effectiveness		
Base case (with some re-specification)		\$████	████	\$████	-
1	ITC OS HR upper limit	\$████	████	\$████	████%
2	Modelling progression-free drugs per cycle	\$████	████	\$████	████%
3	Model pemetrexed based on docetaxel curves (applied non-squamous HR from Scagliotti)	\$████	████	\$████	████%
4	Gompertz for OS pembrolizumab squamous	\$████	████	\$████	████%
5	Mean number of doses Pembrolizumab= 10.2 / D/P=5.3	\$████	████	\$████	████%
6	Time horizon = 5 years	\$████	████	\$████	████%
7	Specificity of PD-L1 testing = █████%	\$████	████	\$████	████%
8	ITC based on non-squamous population	\$████	████	\$████	████%
9	Use of PIVOTAL ongoing disease management costs	\$████	████	\$████	████%
10	OS/PFS models stratified by histology	\$████	████	\$████	████%
11	Discounting=10%	\$████	████	\$████	9%
12	Post-progression treatment*	\$████	████	\$████	████%
13	Model pemetrexed based on docetaxel curves (applied adenocarcinoma HR from Scagliotti)	\$████	████	\$████	████%
14	Discounting=0%	\$████	████	\$████	-████%
15	ITC OS HR lower limit	\$████	████	\$████	-████%
Multivariate analyses					
#2 AND #10		\$████	████	\$████	████%
#2, #10 AND #3		\$████	████	\$████	████%
#2, #10, #3 AND #6		\$████	████	\$████	████%
#2, #10, #3, #6 AND #12		\$████	████	\$████	████%
#2, #10, #3, #6, #12 AND using the parametric model that best fit the pembrolizumab OS squamous curve (Weibull)*		\$████	████	\$████	████%

Note: Analysis 1, 2, 3, 4, 12, 13 and the multivariate analyses were conducted during the evaluation. The base case was re-specified to correct for i) the approach used to determine the proportion of patients who are true positives, false positives, true negatives and false negatives; and ii) drug acquisition costs to be based on the efficient combination of vials, allowable maximum PBS dose and update efficient funding of chemotherapy fees (1 July, 2016).

* Sensitivity analysis assumes that of the patients that uptake post-progression therapy, post-progression treatment is determined by histology. After pembrolizumab treatment, 77.6% of patients (i.e. proportion non-squamous) who uptake post-progression therapy are assumed to receive pemetrexed, and the remaining receive docetaxel. Patients on comparator treatment who received pemetrexed (i.e. non-squamous patients, 77.6%) are assumed to receive docetaxel after disease progression, and vice-versa.

^ Conducting sensitivity analyses #4 from Table D.6.1 would have no effect on the ICER as the KN-010 pembrolizumab OS strong positive (TPS ≥50%) ITT curve is no longer modelled (as per sensitivity analysis #9). Instead, the KN-010 strong positive (TPS ≥50%) squamous data are modelled. The parametric model that best fit these data was a Weibull model.

HR = hazard ratio; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival

Source: Table D.6-1, pp357-8 of the submission

- 6.79 The PSCR (p1) offered a new price for pembrolizumab of \$ [REDACTED] per 50 mg vial to reflect longer time on treatment than was previously estimated. On the basis of 13 administrations of pembrolizumab and 9 administrations of pemetrexed, the PSCR (p8) stated that the resulting ICER was \$45,000 - \$75,000 per QALY. However, verification of the updated assumptions indicated that the resulting ICER was \$45,000 - \$75,000 per QALY.
- 6.80 The PBAC noted that the PSCR changed variables in the economic model and offered a price reduction for pembrolizumab, which resulted in a new verified base case ICER of \$45,000 - \$75,000 per QALY. The PBAC acknowledged that the results of the economic evaluation and sensitivity analyses, with some re-specification made by the evaluation, were not revised to reflect the changes from the PSCR. However, the PBAC considered that the changes introduced by the PSCR had a minor difference on the ICER and so also referred to the sensitivity analyses presented by the commentary around its base case of (\$45,000 - \$75,000 per QALY). The PBAC therefore acknowledged that its reference to the below figures do not reflect the changes from the PSCR, but considered that this did not impact on its overall decision making.
- 6.81 The PBAC noted that the base case ICERs presented by the submission and the commentary were based on the requested TPS $\geq 50\%$ subgroup of patients receiving pembrolizumab. Given the unresolved issues with using PD-L1 expression as a biomarker, the PBAC considered it important that the ICER would increase from \$45,000 - \$75,000 per QALY to \$75,000 - \$105,000 per QALY if all PD-L1 positive patients (TPS $\geq 1\%$) were eligible to receive treatment, and would likely increase further if PD-L1 negative patients were also eligible to receive pembrolizumab.

Drug cost/patient/course: \$ [REDACTED] (revised: \$ [REDACTED])

- 6.82 The submission estimated that the cost per patient per treatment course was \$ [REDACTED] (revised: \$ [REDACTED])^f. The average cost per administration was \$ [REDACTED] (revised: \$ [REDACTED])^g, which was based on an average number of 3.34 vials per patient (including wastage) per administration. Each patient was assumed to have an average of 9.04 administrations (updated to 13.0 in the PSCR), given every three weeks, per treatment course, based on the truncated average treatment cycles in the KN-010 trial. Continuing treatment until progression of disease would increase this estimate.
- 6.83 Comparator treatment cost per patient per course was \$754 (revised: \$757)^h for docetaxel based on 4.78 treatment cycles (as per KN-010), assuming 7.29 20 mg docetaxel vials, and \$14,996 (revised: \$28,062)ⁱ for pemetrexed, assuming 4.78

^f Revised to take into account the proposed price reduction of pembrolizumab (PSCR), updated number of pembrolizumab administrations (PSCR), the maximum dose of pembrolizumab and updated EFC fees (1 July, 2016).

^g Revised to take into account that larger than the allowed maximum dose of pembrolizumab (240mg) was used in the submission's analyses, and the proposed price reduction (PSCR).

^h Revised to take into account the efficient combination of docetaxel vials and updated EFC fees (1 July, 2016).

ⁱ Revised to take into account the updated pemetrexed administrations (PSCR), the maximum dose of pemetrexed and the updated EFC fees (1 July, 2016).

treatment cycles (updated to 9.0 in the PSCR) of 9.55 100 mg pemetrexed vials (including wastage) per cycle.

Estimated extent of use and financial implications

6.84 This submission was not considered by DUSC.

6.85 An epidemiological approach was used in the submission to estimate the number of patients eligible for PD-L1 testing and pembrolizumab treatment each year, over a five-year period. This was based on data presented in the sponsor-commissioned ONCOSight report that estimated the number of Stage IIIB/IV NSCLC patients treated with first-line therapy. A summary of the approach used in the commissioned report is presented in Table 23. The redacted table below shows that at year 5 the estimated number of patients treated with pembrolizumab was less than 10,000 per year.

Table 23: Estimated number of patients who would be tested and who received first-line treatment in year prior to pembrolizumab listing

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
No. prevalent Stage IIIB/IV cases	5,622	-	-	-	-	-
No. incident NSCLC cases	10,399	10,721	11,054	11,396	11,744	12,093
No. incident Stage IIIB/IV NSCLC cases (65%) ^a	6,759	6,969	7,185	7,408	7,634	7,860
No. earlier cases that progress to Stage IIIB/IV	3,833	3,951	4,074	4,200	4,328	4,457
Total patients uptake PD-L1 testing (prevalent year prior + Stage IIIB/IV incident cases)	-	████	████	████	████	████
Revised^a (prevalent year prior + all incident cases)	-	████	████	████	████	████
Population eligible for 1L treatment ^a (incident + progressed cases)	████	████	████	████	████	████
No. that uptake 1L treatment (████%) ^a	████	████	████	████	████	████

^a These estimates were revised to take into account a 10% increase in the number of patients with Stage IIIB/IV disease at diagnosis (65% vs 55%), per the PSCR (p8 and Table 5, p10).

NSCLC = non-small cell lung cancer

Source: ONCOSight report (based on the number of patients in the year before pembrolizumab listing), Appendix 30 of the submission.

6.86 Assumptions used to generate these estimates may not be reasonable as:

- the number of patients who progress to Stage IIIB/IV disease was not adequately described; and
- the proportion who take up first-line treatment (████%) may be an underestimate, as it was assumed that all patients who progress to Stage IIIB/IV develop Stage IV disease.

6.87 Of patients treated in the prior year with first-line therapy, █████% were estimated to have TPS ≥50% PD-L1 expression, based on the proportion of Australian patients screened for KN-001 and KN-010 who strongly expressed PD-L1 (TPS ≥50%). Of all patients screened for KN-001, the proportion with TPS ≥50% was observed to be higher (████%). No rationale was provided in the submission as to why prevalence in the Australian population would differ from the more complete dataset. The financial implications are highly sensitive to changes in the prevalence estimate.

- 6.88 The proportion of patients likely to be treated was disaggregated by histology and by line of therapy, as patients with non-squamous histology who have EGFR or ALK mutations would only be eligible for pembrolizumab at third-line. The introduction of pembrolizumab to the market was assumed to increase second- and third-line treatment uptake from █% and █%, respectively, by █% per annum (see Table 22).
- 6.89 The submission’s estimates for the number of pembrolizumab prescriptions per year are presented in Table 24. The redacted table below shows that at year 5, the estimated number of patients to uptake pembrolizumab would be less than 10,000 per year.

Table 24: Number of patients eligible and uptake pembrolizumab, by line of treatment^a

	Year 1	Year 2	Year 3	Year 4	Year 5
1L treated patients from previous year	█	█	█	█	█
No. patients TPS ≥50% (22.2%)	█	█	█	█	█
No. with squamous histology eligible for 2L (22.4%)	█	█	█	█	█
% of patients that uptake 2L pembrolizumab	█%	█%	█%	█%	█%
No. patients that uptake 2L pembrolizumab	█	█	█	█	█
No. with non-squamous histology (77.6%)	█	█	█	█	█
No. with non-squamous histology eligible for 2L (EGFR or ALK M-: 83.5%)	█	█	█	█	█
% of patients that uptake 2L pembrolizumab	█%	█%	█%	█%	█%
No. patients that uptake 2L pembrolizumab	█	█	█	█	█
No. with non-squamous histology eligible for 3L (EGFR or ALK M+: 16.5%)	█	█	█	█	█
% of patients that uptake 3L pembrolizumab	█%	█%	█%	█%	█%
No. patients that uptake 3L pembrolizumab	█	█	█	█	█
Total patients who uptake pembrolizumab treatment	█	█	█	█	█
Total administrations (9.04 per patient)	█	█	█	█	█
Revised total administrations (13.0 per patient) ^b	█	█	█	█	█

^a These estimates were revised to take into account a 10% increase in the number of patients with Stage IIIB/IV disease at diagnosis (65% vs 55%), per the PSCR (p8 and Table 5, p10).

^b These estimates were also revised to take into account the updated number of administrations of pembrolizumab in the PSCR.

Source: Table E.2-1, pp363-364 of the submission; Table E.2-2, p364 of the submission; Tables E.2-4 and E.2-5, p366 of the submission; and Tables E.2-6 and E.2-7, p368 of the submission; Table E.2-10, p370 of the submission; Table E.2-11, p371 of the submission.

1L = first-line; 2L = second-line; 3L = third-line; ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; PD-L1 = programmed death-ligand 1.

- 6.90 The submission assumed that the number of patients eligible for testing was based on the number of incident Stage IIIB/IV NSCLC cases. In the first year of listing, catch up testing of prevalent cases was also assumed based on the number of prevalent Stage IIIB/IV cases in the year prior to listing. The submission did not include testing patients who progress to Stage IIIB/IV disease from an earlier stage – this increased the number of patients eligible for testing by 26% in the first year, to 40% in subsequent years.

- 6.91 The submission estimated up to 10,000 prescriptions of pembrolizumab dispensed per year, with a cumulative total of 10,000 – 50,000 prescriptions over the five-year period. The updated estimates provided in the PSCR increased the number of prescriptions dispensed per year up to 10,000 – 50,000 and 50,000 – 100,000 over the five-year period.
- 6.92 The submission estimated the net cost of listing pembrolizumab in the PBS/RPBS would be approximately more than \$100 million over the first five years (revised: more than \$100 million). This is likely to be an underestimate, as the number of patients eligible for pembrolizumab may be underestimated, the number of pembrolizumab treatment cycles was likely to be underestimated and cost offsets may be overestimated, as cost savings have been claimed on the basis of reduced pemetrexed and docetaxel use, however, these treatments may be used following treatment with pembrolizumab.
- 6.93 The submission estimated that the overall net cost of PD-L1 testing and pembrolizumab to the Government would be approximately more than \$100 million over the first five years (revised: more than \$100 million) as presented in Table 25.

Table 25: Cost of PD-L1 testing and pembrolizumab treatment to the MBS and PBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Cost of PD-L1 testing Revised (i)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Administration & management costs Revised (ii)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to the MBS Revised	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost of pembrolizumab to the PBS/RPBS Revised (ii, iii, iv, vii and viii)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost offsets to the PBS/RPBS Revised (ii, v, vi, vii and viii)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total cost to the PBS/RPBS Revised^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to government Revised^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

^a These estimates were revised to take into account i) testing irrespective of disease stage; ii) the updated administrations of pembrolizumab (13.0) and pemetrexed (9.0) in the PSCR; iii) the proposed price reduction of pembrolizumab in the PSCR; iv) the maximum dose of pembrolizumab; v) the efficient combination of docetaxel vials; vi) the maximum dose of pemetrexed; vii) the updated Efficient Funding of Chemotherapy fees (1 July, 2016), and viii) 10% increase in the number of patients with Stage IIIB/IV disease at diagnosis (65% vs 55%) in the PSCR, as denoted.

Source: Table E.5-9, p392 of the submission and Table E.4-1, p387 of the submission.

- 6.94 There is potential for the net cost/year for the Government to be greater than the estimate in the submission due to underestimated costs to the MBS and PBS, and overestimated cost offsets.
- 6.95 As the proposed TGA indication of pembrolizumab is for use in patients who express PD-L1, there is potential for usage outside of the requested listing in patients who weakly express PD-L1 (TPS 1–49%). There may be potential for off-label use of pembrolizumab in an unselected population – particularly in patients with squamous

histology as the evidence does not conclusively support treatment effect modification by PD-L1 status, and if nivolumab (another PD-1 inhibitor) is listed in the PBS, as has been requested, without reference to PD-L1 status. The PSCR (p8) proposed that the risk of leakage be addressed through a Risk Share Arrangement.

- 6.96 The PBAC noted that in the scenario analysis where a PD-L1 expression threshold of TPS $\geq 1\%$ was used instead of the base case of TPS $\geq 50\%$, the overall net cost of PD-L1 testing and pembrolizumab to the Government would be approximately more than \$100 million over the first five years of listing (not including the updated figures from the PSCR, which would increase the estimated 5-year financial estimates).

Quality Use of Medicines

- 6.97 Although not the recommended dose in the pembrolizumab draft Product Information for NSCLC, there was some indication from Trial KN-010 that pembrolizumab 10 mg/kg was associated with larger median OS gain versus docetaxel compared to the pembrolizumab 2 mg/kg dose. Whether future regulatory decisions and clinical practice would conform to this evidence and whether there would be any impact on quality use of medicine, economic and financial issues remained uncertain. Similar issues would arise if shifting to a 200 mg dose without reference to body weight.

Financial Management – Risk Sharing Arrangements

- 6.98 The submission proposed a Special Pricing Arrangement (SPA) where the published price is greater than the effective price.

Other relevant factors

Impact of patient age on treatment response

- 6.99 The ESCs discussed whether the OS outcomes varied by age and whether this would represent applicability issues to the potential PBS population who might be substantially older on average than the patients enrolled in KN-010 (median age of pembrolizumab patients = 63 years). The HR for OS of pembrolizumab 2 mg/kg versus docetaxel from KN-010 is presented in Table 26.

Table 26: Pembrolizumab KN-010 (regardless of histology), OS HR by age (in years) for pembrolizumab, 2 mg/kg Q3W vs docetaxel

Population	n events/N	HR (95% CI)
ITT (PD-L1 TPS ≥1%)		
<65	228/410	0.69 (0.53, 0.91)
≥65	137/277	0.78 (0.55, 1.10)
Subgroup: TPS ≥50%		
<65	96/180	0.63 (0.41, 0.95)
≥65	48/111	0.43 (0.23, 0.82)
Subgroup: TPS 1–49%		
<65	132/230	0.70 (0.49, 0.99)
≥65	89/166	0.99 (0.65, 1.52)

Database cut-off: 30 September 2015

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival; PD-L1 = programmed death ligand 1; Q3W = every three weeks; TPS = tumour proportion score.

- 6.100 KN-010 did not stratify by age at randomisation and such analyses are only exploratory. Interpretation of these results should consider the inherent caveats of the subgroup analyses. There are no data by age and histology subtype.

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

7 PBAC Outcome

- 7.1 The PBAC decided not to recommend that pembrolizumab be listed in the PBS for the treatment of PD-L1 positive NSCLC on the basis of unfavourable and uncertain cost-effectiveness.
- 7.2 The PBAC recognised that there is a clinical need for new treatments for patients with NSCLC, and that there is a clinical place for pembrolizumab in this population. The PBAC noted that the submission requested a second- and third-line PBS listing for pembrolizumab, following progression on or after platinum-based chemotherapy, for squamous and non-squamous NSCLC respectively.
- 7.3 The PBAC advised the following with regard to the requested restriction:
- that there was uncertainty in selecting a PD-L1 expression threshold to define an optimal patient population mostly likely to respond to treatment;
 - that the continuing treatment restriction would need to contain the criterion already used for PD-1 inhibitors requiring stable or responding disease; and
 - that the patient's performance status would need to be 0 or 1, consistent with the eligibility criteria of the key clinical trial.
- 7.4 The PBAC considered that the use of the proposed TPS ≥50% threshold from PD-L1 testing to help determine eligibility of patients with NSCLC to receive pembrolizumab was not adequately justified. The PBAC noted the rationale provided in the pre-PBAC response and during the sponsor hearing regarding the use of ROC curves, however, considered that this was not an appropriate methodology to determine an optimal PD-L1 threshold. The PBAC also considered that there were important unresolved

issues regarding PD-L1 testing which have consequences for this co-dependent submission, including the optimal threshold for PD-L1 positivity, the predictive effect of PD-L1 expression, and thus the extent of incremental effectiveness (and cost-effectiveness) of pembrolizumab over its comparators. As these issues were relevant to MSAC, PBAC decided that it should await MSAC's assessment before first drawing any conclusions on the usefulness of PD-L1 testing as a means of selecting patients for treatment with pembrolizumab.

- 7.5 The submission nominated docetaxel and pemetrexed as the main comparator for patients with squamous and non-squamous NSCLC, respectively. The PBAC considered that these were the appropriate comparators.
- 7.6 The PBAC considered that a PD-L1 TPS threshold of 50% was weakly shown to be a treatment effect modifier based on the plausibility of treatment effect variation, pre-specification of this analysis, and statistical analysis of the ratio of HRs across subgroups categorised as TPS $\geq 50\%$ vs TPS 1–49%.
- 7.7 The PBAC noted that, although the comparison between pembrolizumab and docetaxel for squamous NSCLC was based on direct evidence, the evidence was limited, due to the smaller proportion (21%) of patients with squamous NSCLC in the KN-010 trial. However, the PBAC considered that the effectiveness of pembrolizumab was likely to be similar for both squamous and non-squamous PD-L1 positive NSCLC.
- 7.8 The PBAC also noted that the submission's claim that pembrolizumab was of superior effectiveness over pemetrexed in patients with non-squamous NSCLC was based on indirect evidence, and was associated with transitivity issues. The PBAC noted that the indirect comparison for the subgroup of patients with $\geq 50\%$ TPS showed that pembrolizumab was of superior efficacy over pemetrexed, but that the ITT analysis using all PD-L1 positive (TPS $\geq 1\%$) patients did not show a clear gain in OS with pembrolizumab over pemetrexed as the confidence interval crossed 1.
- 7.9 The PBAC concluded that pembrolizumab was more effective than docetaxel and pemetrexed, but that the magnitude of the gain in effectiveness over pemetrexed was less clear due to the need to conduct an indirect comparison.
- 7.10 The PBAC considered that pembrolizumab would likely be better tolerated overall than docetaxel or pemetrexed, however, was more likely to increase the risk of immune-related adverse events.
- 7.11 The PBAC noted that the calculations for the incremental cost per QALY gained of \$45,000 - \$75,000 from the PSCR-proposed changes for pembrolizumab over standard of care (docetaxel or pemetrexed) for NSCLC patients with strong PD-L1 expression (TPS $\geq 50\%$) had been independently verified. However, the Committee advised that this ICER/QALY was high, and was likely to be significantly underestimated due to several concerns raised by the ESCs regarding the economic model. The PBAC noted the ESCs' concern that the clinical claims made in the submission, which were used as the basis for economic modelling, were not substantiated by the clinical evidence presented in the submission. The PBAC considered that the uncertainty in the clinical evidence resulted in uncertainty in the results of the economic model. The PBAC agreed with the ESCs that a 5-year time

horizon would be more appropriate and noted that the 7-year time horizon used by the submission underestimated the ICER. The PBAC also noted that, if the criterion for treatment eligibility was changed from TPS $\geq 50\%$ to include all of the PD-L1 positive population (TPS $\geq 1\%$), the ICER would increase substantially, and would be unacceptably high.

7.12 The PBAC noted that the estimated overall net cost of PD-L1 testing and pembrolizumab for NSCLC to the Government would be approximately more than \$100 million over five years, if only patients with strong PD-L1 expression (TPS $\geq 50\%$) were treated. The PBAC further noted that if all PD-L1 positive patients (TPS $\geq 1\%$) were treated, the financial implications to Government would more than double over five years.

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

Outcome:

Rejected

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

The sponsor will continue to work with the government to ensure access to pembrolizumab for appropriate patients as soon as possible.