

## 6.06 Pembrolizumab, Injection, 100 mg/4 mL, Keytruda<sup>®</sup>, Merck Sharp & Dohme (Australia)

### 1 PURPOSE OF APPLICATION

- 1.1 The submission requested a S100 Efficient Funding of Chemotherapy Authority Required (Streamlined) listing for pembrolizumab to be used in combination with cisplatin/carboplatin and pemetrexed (referred to as pembrolizumab+platinum+pemetrexed herein) for treatment of patients with Stage IV non-squamous (NSQ), epidermal growth factor receptor (EGFR) wild type and anaplastic lymphoma kinase (ALK) translocation negative non-small cell lung cancer (NSCLC), with an ECOG status of 0 or 1. The PBAC has not considered pembrolizumab+platinum+pemetrexed previously. However, pembrolizumab monotherapy is subsidised for use in patients with Stage IV, EGFR wild type and ALK translocation negative NSCLC with an ECOG status of 0 or 1 AND programmed death ligand 1(PD-L1) tumour proportion score (TPS)  $\geq 50\%$  (both NSQ and squamous (SQ)).
- 1.2 The requested basis for listing was a cost-effectiveness analysis compared with two comparators, which differed depending on the patient's PD-L1 TPS status (<50% or  $\geq 50\%$ ).

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

Component	Description
Population	Patients with Stage IV NSQ, EGFR wild type and ALK translocation negative NSCLC
Intervention	Pembrolizumab + platinum chemotherapy + pemetrexed
Comparator	For patients with PD-L1 TPS <50%: platinum doublet chemotherapy followed by PD-(L)1 therapy (revised in pre-PBAC response to include "followed by PD-(L)1 therapy".) For patients with PD-L1 TPS $\geq 50\%$ : pembrolizumab monotherapy
Outcomes	OS, PFS and quality of life
Clinical claim	Clinically and statistically significant improvements in OS (HR = 0.57 vs platinum doublet and HR = [REDACTED] in indirect comparison vs pembrolizumab monotherapy).

Abbreviations: NSQ = non-squamous, NSCLC = non-small cell lung cancer, EGFR = Epidermal Growth Factor Receptor, ALK = Anaplastic lymphoma kinase, PD-L1 = programmed death ligand 1, TPS = tumour proportion score, OS = overall survival, PFS = progression free survival; TPS is a measure of PD- L1 protein expression, which is the percentage of viable tumour cells showing partial or complete membrane staining. The specimen should be considered PD-L1 positive if TPS  $\geq 50\%$  of the viable tumour cells exhibit membrane staining at any intensity.

Source: constructed using information from p1 of the submission.

- 1.3 In the pre-PBAC response, the sponsor acknowledged that a statistically significant benefit of pembrolizumab+platinum+pemetrexed compared with pembrolizumab monotherapy had not been established. The sponsor requested that PBAC defer its

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consideration of the subsidy request for the PD-L1 TPS  $\geq$ 50% subgroup to allow the clinical data to mature. The PBAC declined this request.

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

## 2 REQUESTED LISTING

2.1 The proposed initial treatment restriction, as presented in the pre-PBAC response, is provided below. The proposed criterion restricting treatment to patients with PD-L1 TPS <50%, added during the pre-PBAC response, is underlined.

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Pembrolizumab 100 mg/4 mL injection, 4 mL vial	200 mg	3	\$ [REDACTED] (Private Hospital) \$ [REDACTED] (Public Hospital)	Keytruda, Merck Sharp and Dohme Ltd.

<b>Category / Program</b>	Section 100 – Efficient funding of Chemotherapy (Public and Private Hospital)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Stage IV (metastatic)
<b>Condition:</b>	Non squamous non-small cell lung cancer
<b>PBS Indication:</b>	Stage IV (metastatic) non squamous non-small cell lung cancer
<b>Treatment phase:</b>	Initial treatment
<b>Restriction:</b>	<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
<b>Clinical criteria:</b>	The patient must not have received prior systemic treatment for this condition in the metastatic setting AND The condition must be non-squamous type non-small cell lung cancer AND <u>The condition must express programmed cell death ligand 1 (PD-L1) with a tumour proportion score of less than 50% in the tumour sample [inserted in Pre-PBAC response]</u> AND The treatment must be in combination with pemetrexed and carboplatin or cisplatin. AND Patient must have a WHO performance status score of 0 or 1, AND The treatment with pembrolizumab must not exceed a total of 6 doses at a dose of 200 mg every 3 weeks.
<b>Population criteria:</b>	Patient must have no evidence of an activating epidermal growth factor gene or of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material

<b>Administrative Advice:</b>	<p>No increase in the maximum number of repeats will be authorised.</p> <p>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.</p> <p>Special pricing arrangement apply</p>
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- 2.2 The proposed continuing treatment restriction and grandfathering restriction are presented in the pre-PBAC response.
- 2.3 A special pricing arrangement (SPA) was proposed which included a lower effective price for pembrolizumab when used in combination with platinum doublet which was dependent on the patient population being treated (TPS <50 or ≥50%; percentages consistent with the proportional split assumed in the pembrolizumab monotherapy submission) as well as an annual subsidisation cap. The effective prices proposed in the initial submission are summarised in Table 2.

**Table 2: Effective price for pembrolizumab when used in combination with platinum doublet**

	Effective dispensed price	Proportion of patients
PD-L1 TPS <50%	\$ [REDACTED] per 100mg vial	71.5%
PD-L1 TPS ≥50%	\$ [REDACTED] per 100mg vial	28.5%
Weighted	\$ [REDACTED] per 100mg vial	100%
Dispensed Price for Maximum Amount	\$ [REDACTED] for 200mg	100%

Source: Table 3.6-1, p142 of the submission

The prices are relevant to the submission, and do not account for changes made in the pre-PBAC response.

- 2.4 The ESC noted that the effective dispensed price that has been agreed for pembrolizumab monotherapy in the PDL1 TPS≥50% population is \$ [REDACTED] per 200 mg dose.
- 2.5 In the pre-PBAC response, the proposed effective dispensed price for pembrolizumab was \$ [REDACTED] per 200mg dose for the PD-L1 TPS <50% subgroup. No change in the proposed effective price for the PD-L1 TPS ≥50% subgroup was made, as the pre-PBAC response requested the PBAC defer its consideration of this part of the listing request.

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

### 3 BACKGROUND

#### **Registration status**

- 3.1 Pembrolizumab, when used with pemetrexed + platinum chemotherapy, was approved by the TGA on 12 June 2018 for the first-line treatment of patients with metastatic, non-squamous NSCLC.

### **Previous PBAC consideration**

- 3.2 The PBAC has not previously considered pembrolizumab when used with pemetrexed + platinum chemotherapy for this condition.

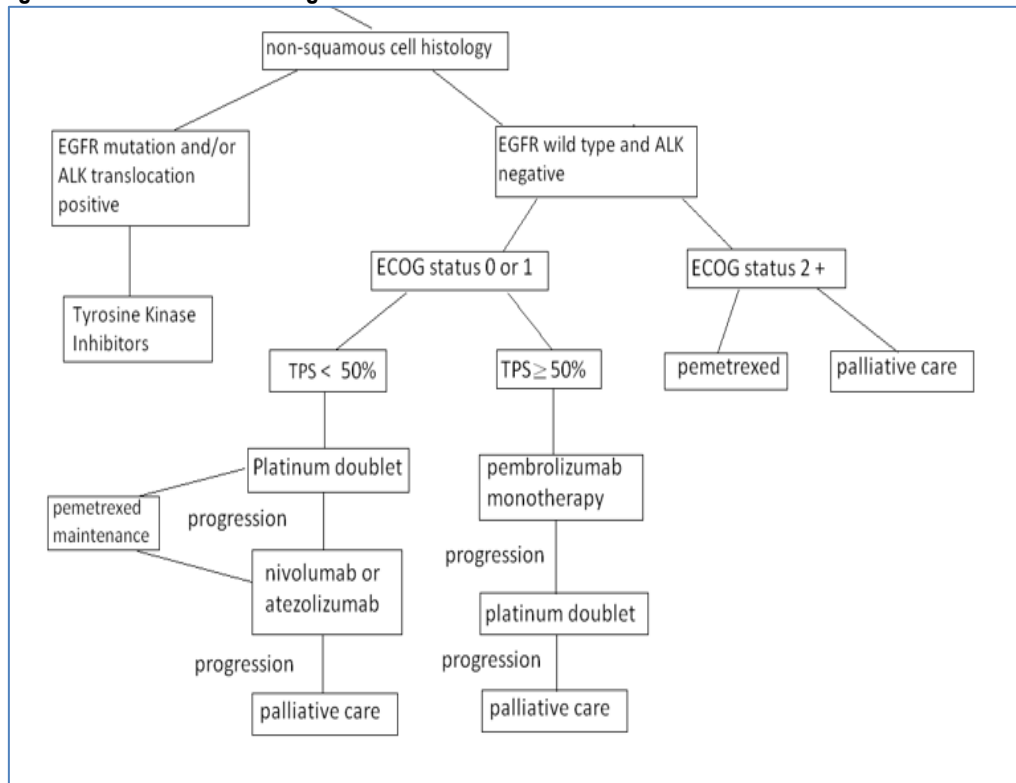
## **4 POPULATION AND DISEASE**

- 4.1 Lung cancer is the leading cause of death and the fifth most common cancer diagnosed in Australia. NSCLC is the most common type of lung cancer and accounts for around 80% of all cases. The 1-year and 5-year relative survival at diagnosis for all Australian lung cancer patients were estimated as 41.6% and 15.8%, respectively (AIHW 2017). Stage IV (metastatic) NSCLC is the most advanced form of cancer.

## **5 COMPARATOR**

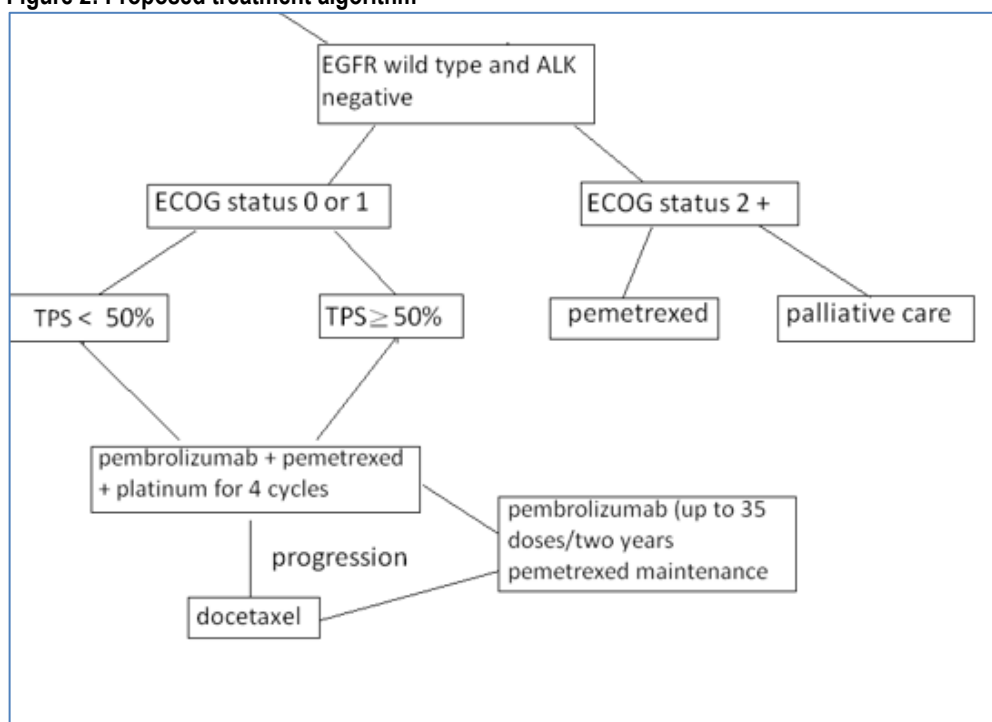
- 5.1 The submission nominated two comparators for two different groups of patients depending on the patient's PD-L1 TPS status.
- for patients with PD-L1 TPS <50%, the nominated comparator was cisplatin/carboplatin + pemetrexed (referred to as platinum doublet or SoC herein); and
  - for patients with PD-L1 ≥50%, the nominated comparator was pembrolizumab monotherapy.
- 5.2 Consistent with the advice of the ESC, the pre-PBAC response revised the comparator for patients with PD-L1 TPS <50% to be platinum doublet followed by a PD-(L)1 inhibitor.
- 5.3 The PBAC noted that with the listing of pembrolizumab monotherapy on the PBS on 1 November 2018 the treatment algorithm is as depicted in Figure 1.

Figure 1: Current treatment algorithm



5.4 The PBAC noted that if pembrolizumab+platinum+pemetrexed were to become available on the PBS, the treatment algorithm for the majority of patients will be as depicted in Figure 2.

Figure 2: Proposed treatment algorithm



- 5.5 The PBAC therefore agreed with the submission’s re-specification of the comparator for the PD-L1 TPS <50% group and further considered that the comparator for patients in the PD-L1 ≥50% should more appropriately be pembrolizumab monotherapy followed by a platinum doublet.
- 5.6 The PBAC noted that with respect to the comparator for the PD-L1 TPS <50% group the pre-PBAC response states “the subsequent use of nivolumab or atezolizumab was reflected in the treatment algorithm (Figure 1.2.1, July 2018 submission), and, throughout the submission Pembro Combo was compared to platinum + pemetrexed followed by PD1-/PD-L1. In Section 2, the KN189 trial compared Pembro Combo to platinum doublet followed by a PD-1/PD-L1 inhibitor, as the trial design pre-specified crossover from platinum + pemetrexed to pembrolizumab and patients on a platinum + pemetrexed also went on a PD-1/PD-L1 outside of the trial. After 10.5 months median follow up, 84.6% (n=83/96) of patients in the platinum + pemetrexed arm who went on subsequent therapy went on a PD-1 inhibitor, reflective of the treatment algorithm in the Australian setting. In Section 3 and 4 the costs and benefits of 2L PD-1/PD-L1 treatment were considered in the comparator arm of the economic evaluation and budget impact model.” (Pre-PBAC response p1).
- 5.7 However, the pre-PBAC response did not provide information on how many patients in the platinum+pemetrexed arm of KN189 who had a PD-L1 TPS < 50% were crossed over and whether the trial was sufficiently powered to support a conclusion that pembrolizumab+platinum+pemetrexed is superior in effectiveness to platinum+pemetrexed, and if so, what the magnitude of the benefit is.

- 5.8 The PBAC noted that pemetrexed is not currently PBS-listed for first-line treatment of NSQ NSCLC, but a recent PBAC recommendation for derestriction of pemetrexed would permit its use in the proposed setting. The most commonly used platinum doublet in Australia is carboplatin + gemcitabine based on the PivOTAL study (an international retrospective cohort of systemic therapy treatment in patients with stage IIIb and IV NSCLC that included 163 Australian patients). Nonetheless, the eviQ protocol<sup>1</sup> notes that in NSCLC patients with non-squamous histology, pemetrexed/cisplatin conferred superior median overall survival (11 months) compared with other regimens including gemcitabine/carboplatin (8.3 months). Therefore the submission's use of platinum + pemetrexed in both the comparator and in the pembrolizumab+platinum+pemetrexed regimen was appropriate.
- 5.9 The PBAC recalled it had previously accepted all platinum doublets to be comparable and clinically non-inferior to each other (e.g. gefitinib PSD July 2013).

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

## 6 CONSIDERATION OF THE EVIDENCE

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (2) and a health care professional (1) via the Consumer Comments facility on the PBS website. The comments described cases of patients who have benefited from the use of pembrolizumab and stated that the benefits in the metastatic setting are established.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for pembrolizumab+platinum+pemetrexed in patients with PD-L1 TPS 1-49% on the basis of PFS (OS was noted to be immature). MOGA also expressed its support in patients with PD-L1 TPS <1% on the basis of OS. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab+platinum+pemetrexed for both PD-L1 TPS 1-49% and <1%, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>[1]</sup>, based on a comparison with chemotherapy<sup>2</sup>.
- 6.4 MOGA refrained from including the PD-L1 TPS ≥50% subgroup in its letter as the current published evidence does not compare pembrolizumab+platinum+pemetrexed

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<sup>1</sup> <https://www.eviq.org.au/medical-oncology/respiratory/non-small-cell-lung-cancer/88-nsclc-metastatic-cisplatin-and-pemetrexed#18342> accessed 27/7/18

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

with pembrolizumab monotherapy, which it deems to be the appropriate comparator.

### Clinical trials

6.5 The submission was based on:

- one head-to-head randomised trial (KN189) comparing pembrolizumab+platinum+pemetrexed versus platinum doublet; and
- one supplementary randomised trial (KN024) comparing pembrolizumab monotherapy versus platinum doublet, used in an indirect comparison with KN189. The PBAC previously considered KN024 in the submission of pembrolizumab monotherapy for first-line treatment of Stage IV NSCLC in patients with EGFR wild type, ALK translocation negative, ECOG status 0 or 1 and PD-L1 TPS  $\geq 50\%$  (March 2017, November 2017, March 2018 and July 2018). An additional trial, KN042, was identified but not included in the initial submission as complete study results from this trial were not available at the time the submission was lodged for PBAC consideration. The sponsor subsequently included information from the February 2018 data cut-off for KN042 in its pre-subcommittee response (PSCR).

6.6 Details of the trials presented in the submission are provided in Table 3.

**Table 3: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
Pembrolizumab+platinum+pemetrexed versus platinum doublet		
KN189	Study of Platinum+Pemetrexed Chemotherapy With or Without Pembrolizumab (MK-3475) in Participants With First Line Metastatic Non-squamous Non-small Cell Lung Cancer (MK-3475-189/KEYNOTE-189)  Gandhi et al, 2018, Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer.	Date not provided  NEJM 2018; <a href="https://doi.org/10.1056/NEJMoa1801005">https://doi.org/10.1056/NEJMoa1801005</a>
Pembrolizumab monotherapy versus platinum doublet		
KN024	A Randomized Open-Label Phase III Trial of Pembrolizumab versus (vs.) Platinum based Chemotherapy in First-Line (1L) Subjects with Programmed Cell Death 1 Ligand (PD-L1) Strong Metastatic NSCLC  Reck et al, 2016 Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer	11 July 2016  NEJM 2016 Nov 10; 375(19):1823-1833. Epub 2016 Oct 8

Source: Table 2.2-1, p39-40 of the submission

6.7 Different comparisons were presented by the submission for patients with PD-L1 TPS  $< 50\%$  and PD-L1  $\geq 50\%$ :

- Direct evidence from the subgroup of patients with PD-L1 TPS  $< 50\%$  in KN189 was used to inform relative efficacy of pembrolizumab+platinum+pemetrexed to platinum doublet; and
- An indirect comparison between the subgroup of patients with PD-L1 TPS  $\geq 50\%$  in KN189 and patients with non-squamous histology who were treated with platinum+pemetrexed in KN024 using platinum doublet as a common reference

was used to inform relative efficacy of pembrolizumab+platinum+pemetrexed to pembrolizumab monotherapy.

6.8 The population in each comparison is indicated in Table 4 with shading.

**Table 4: Treatment arms of the KN189 and KN024 trials used to inform the clinical claims made by the submission**

Comparison	KN189 (N=616), all NSQ				KN024 (N=305), all ≥50%			
	Pembro+plat+peme		Chemotherapy		Pembro mono		Chemotherapy	
	<50%	≥50%	<50%	≥50%	SQ	NSQ	SQ	NSQ
Pembro+plat+peme v SOC (<50%)	n=255		n=121		-	-	-	-
Pembro+plat+peme v pembro mono (≥50%)		n=132		n=70	n=29	n=97 <sup>a</sup>	n=27	n=102 <sup>a</sup>

<sup>a</sup> The number of patients with non-squamous histology in KN024 in the submission were different to the publication, which reports 125 NSQ in pembrolizumab and 124 in chemotherapy. However only patients treated with pemetrexed (n=199) were included in the submission; <50% and ≥50% refer to PD-L1 TPS expression subgroups; SQ and NSQ refer to squamous and non-squamous subgroups, respectively; Pembro+plat+peme = pembrolizumab+platinum+pemetrexed; Shaded cells represent subgroups used in the comparisons; Source: Table 2.6-10, p87-88 of the submission and Reck et al 2016

6.9 The key features of the randomised trial and indirect comparison are summarised in Table 5.

**Table 5: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Pembrolizumab+platinum+pemetrexed versus platinum doublet (TPS &lt;50% subgroup)</b>						
KN189	376 (ITT 616)	R, DB Median 10.5mths	Low, planned subgroup analysis	Untreated (first-line) NSQ NSCLC, EGFR and ALK negative ECOG 0 or 1 and TPS <50%	OS,PFS	Both OS and PFS as well as time on treatment used in model for patients with TPS <50%
<b>Pembrolizumab+platinum+pemetrexed versus pembrolizumab monotherapy, platinum doublet common reference (TPS ≥50% indirect comparison)</b>						
Pembrolizumab+platinum+pemetrexed versus platinum doublet						
KN189	202 (ITT 616)	R, DB Median 10.5mths	Low, planned subgroup analysis	Untreated (first-line) NSQ NSCLC, EGFR and ALK negative ECOG 0 or 1 and TPS ≥50%	OS,PFS	Both OS and PFS as well as time on treatment used in model for patients with TPS ≥50%
Pembrolizumab monotherapy versus platinum doublet						
KN024	199 (ITT 305)	R, OL Median 11.2 mths	Low; OS is objective outcome	Untreated (first-line) NSCLC, EGFR and ALK negative ECOG 0 or 1 and TPS ≥50%	OS, PFS	Only NSQ subgroup treated with platinum+pemetrexed used in TPS ≥50% model

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised. ITT = intention to treat, NSQ = non squamous, NSCLC = non-small cell lung cancer, EGFR = epidermal growth factor receptor, ALK = anaplastic lymphoma kinase, ECOG = Eastern Cooperative Oncology Group, TPS = Tumour proportion score  
Source: Table 2.4-3, and table 2.4-4, p47, table 2.6-7, p84 of the submission and p78-83 of the submission

6.10 The submission (p86) claimed that the design, patient characteristics and outcomes of KN189 and KN024 were comparable and therefore the trials can be considered exchangeable. The PBAC considered that this may not be accurate, as a higher proportion of patients treated with pembrolizumab+platinum+pemetrexed in KN189 had a baseline ECOG status of 0 (██████%) compared to the other three treatment groups in the indirect comparison (██████-██████%). Patients enrolled in KN189 were also

less likely to be classified as M1B in distant metastatic staging (~25%) compared to patients enrolled in KN024 (~█%), indicating that a substantially larger proportion of patients in the latter group had metastatic disease in distant organs (brain, liver, bone, etc.). To address this, the submission used several methods to weight and adjust for cross over within the trials. Patients in the “control” (platinum doublet/SoC) group in KN024 also had significantly better OS and PFS results than patients in the “control” group in KN189 at the time of data cut off, with a significant degree of separation between the two control groups in the OS (and PFS) Kaplan-Meier curve, with the curves never crossing over or overlapping between 3-15 months (see Figure 3).

- 6.11 The indirect comparison was performed on the hazard ratio (HR) using the Bucher method after adjusting population and treatment arms using Inverse Probability of Treatment Weighting (IPTW). A propensity score (the probability of a patient receiving one of four treatments (pembrolizumab+platinum+pemetrexed, pembrolizumab monotherapy or platinum doublet in either KN189 or KN024), was estimated for each patient using multivariate logistic regression based on the following covariates: platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current), ECOG PS (0 vs. 1), age, gender, metastatic stage M1B (yes vs. no), brain metastasis (yes vs. no), and region (Europe, North America, Rest of World). The weighting derived from the propensity score was then applied to the indirect comparison. The submission considered this adjustment was necessary given the differences noted above.
- 6.12 The submission also included three other alternative methods to estimate the efficacy whilst adjusting for the crossover from platinum doublet/SoC to pembrolizumab or PD-L1/PD-1 checkpoint inhibitors, using a two-stage analysis, a Rank-Preserving Structure Failure Time (RPSFT) model or an Inverse Probability of Censoring Weighting (IPCW) model.

## ***Comparative effectiveness***

### **PD-L1 TPS <50% patient subgroup**

#### **Direct comparison of pembrolizumab+platinum+pemetrexed versus platinum doublet**

- 6.13 The results for the ITT and PD-L1 TPS <50% and ≥50% populations from the direct randomised KN189 trial are presented in Table 6. Kaplan-Meier curves for the ITT population (Figure 3) and PD-L1 TPS <50% (Figure 4) in KN189 are also presented below.
- 6.14 A statistically significant improvement in overall and progression free survival was reported for the ITT and PD-L1 TPS <50% and ≥50% populations treated with pembrolizumab+platinum+pemetrexed compared with platinum doublet.

**Table 6: Overall survival and progression free survival results in KN189**

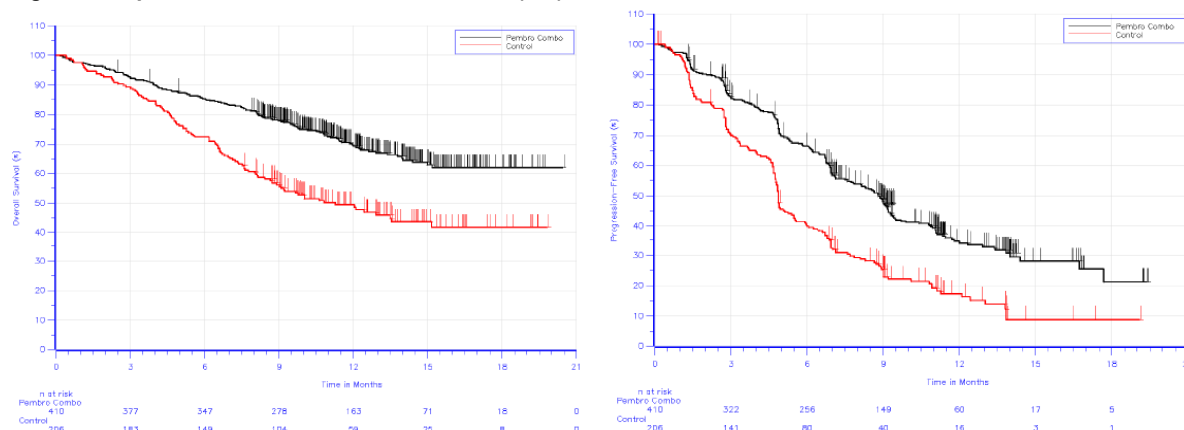
	Pembro+plat+peme	Platinum doublet/SoC	Hazard ratio <sup>a</sup>
<b>Overall survival</b>			
All patients			
No. of deaths at cutoff (~21 months)	127/410 (31.0)	108/206 (52.4)	<b>0.49 (0.38, 0.64)</b>
Median OS in months (95%CI)	Not reached	11.3 (8.7, 15.1)	
PD-L1 TPS <50%			
No. of deaths at cutoff (~21 months)	██████████	██████████	██████████
Median OS in months (95%CI)	██████████	██████████	
PD-L1 TPS ≥50%			
No. of deaths at cutoff (~21 months)	██████████	██████████	<b>0.42 (0.26, 0.68)</b>
Median OS in months (95%CI)	██████████	██████████	
<b>Progression free survival</b>			
All patients			
No. of deaths/progressed at cutoff (~21 months)	244/410 (59.5)	166/206 (80.6)	<b>0.52 (0.43, 0.64)</b>
Median PFS in months (95%CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)	
PD-L1 TPS <50%			
No. of deaths/progressed at cutoff (~21 months)	██████████	██████████	██████████
Median PFS in months (95%CI)	██████████	██████████	
PD-L1 TPS ≥50%			
No. of deaths/progressed at cutoff (~21 months)	██████████	██████████	<b>0.36 (0.25, 0.52)</b>
Median PFS in months (95%CI)	██████████	██████████	

<sup>a</sup> Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).

Pembro+plat+peme = pembrolizumab+platinum+pemetrexed; OS = overall survival, SoC = standard of care, NR = not reported

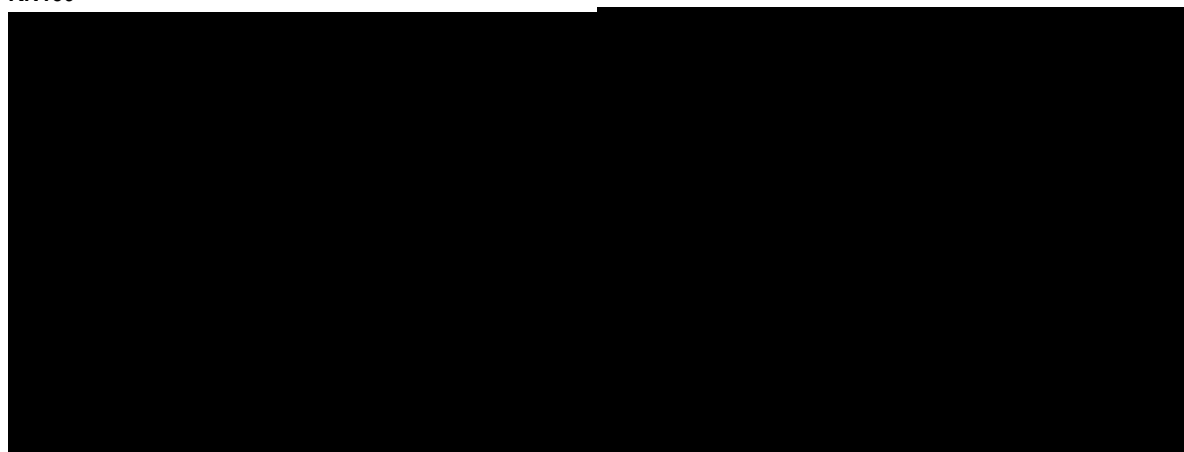
Source: Table 2.6-2, pp72-73 and 2.6-3 pp74-75 of the submission

Figure 3: Kaplan-Meier curve for overall survival (left) and progression-free survival (right) in KN189 ITT population



Source: Figure 2.5-1, p54 and Figure 2.5-3, p56 of the submission

Figure 4: Kaplan-Meier estimates for overall survival (left) and progression-free survival (right) in PD-L1 TPS <50% in KN189



Source: Figure 2.6-2, p73 and Figure 4, p18 in Appendix 13 of the submission

6.15 In the PD-L1 TPS <50% subgroup in KN189, patients treated with pembrolizumab+platinum+pemetrexed were observed to have statistically significantly longer OS (HR [REDACTED], 95% CI: [REDACTED], [REDACTED]) and PFS (HR [REDACTED], 95% CI: [REDACTED], [REDACTED]) compared to patients treated with platinum doublet. It is unclear if the trial was powered to detect differences in the subgroups as the overall power calculation for KN189 (N=570) was based on the whole population irrespective of PD-L1 TPS status, though the subgroup analyses for PD-L1 TPS <50% and TPS ≥50% appears to have been pre-planned at the protocol stage.

**PD-L1 TPS ≥50% patient subgroup**

**Indirect comparison of pembrolizumab+platinum+pemetrexed versus pembrolizumab monotherapy**

6.16 The results of the submission’s indirect comparison in patients with PD-L1 TPS ≥50% are presented in Table 7 (overall survival) and Table 8 (progression free survival). No

Kaplan-Meier curves for patients with PD-L1 TPS  $\geq 50\%$  were presented in the submission. Instead, a comparison of the OS and PFS curves in the ITT population in KN189 and KN024 was presented (Figure 5).

**Table 7: Results of the indirect comparison for overall survival, adjusted by weights**

Trial	Outcome	Pembro+plat+peme n/N (%)	Platinum doublet n/N (%)	Absolute difference	HR (95% CI)
KN189 <sup>a</sup>	Deaths	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>	-
	Median months OS (range) <sup>c</sup>	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>
		Pembrolizumab monotherapy n/N (%)	Platinum doublet <sup>d</sup> n/N (%)	Absolute difference	HR (95% CI)
KN024 <sup>b</sup>	Deaths	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>
	Median months OS (range) <sup>c</sup>	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>
<b>Indirect comparison pembrolizumab+platinum+pemetrexed vs. pembrolizumab monotherapy</b> IPTW weighting only					<b>██████████</b>
2 stage analysis (cross over from platinum doublet to pembrolizumab only)					<b>██████████</b>
2 stage analysis (cross over from platinum doublet to all PD-L1/PD-1 checkpoint inhibitors)					<b>██████████</b>
RPSFT model (cross over from platinum doublet to pembrolizumab only)					<b>██████████</b>
RPSFT model (cross over from platinum doublet to all PD-L1/PD-1 checkpoint inhibitors)					<b>██████████</b>
IPCW model (cross over from platinum doublet to pembrolizumab only)					<b>██████████</b>
IPCW model (cross over from platinum doublet to all PD-L1/PD-1 checkpoint inhibitors)					<b>██████████</b>

<sup>a</sup> Subgroup of patients with PD-L1 Tumour Proportion Score (TPS)  $\geq 50\%$  only

<sup>b</sup> Subgroup of patients with non-squamous histology only

<sup>c</sup> Median for comparator reported for IPTW weighting only

<sup>d</sup> Subgroup of patients treated with cisplatin + pemetrexed or carboplatin + pemetrexed only

Pembro+plat+peme = pembrolizumab+platinum+pemetrexed, OS = overall survival; HR = hazard ratio; NR = not reached; CI = confidence interval, IPTW = Inverse Probability of Treatment Weighting, PD-L1 = Programmed cell Death Ligand 1; PD-1 = Programmed cell Death receptor-1, RPSFT = Rank-Preserving Structure Failure Time, IPCW = Inverse Probability of Censoring Weighting

Figures in bold indicate statistically significant differences

Source: Table 2.6-11, p90 of the submission and Table 7-12, p19-24 of Appendix 14 to the submission

**Table 8: Results of the indirect comparison for progression free survival, adjusted by weights**

Trial	Outcome	Pembro+plat+peme n/N (%)	Platinum doublet n/N (%)	Absolute difference	HR (95% CI)
KN189 <sup>a</sup>	Progressed	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>
	Median months PFS (range) <sup>c</sup>	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>
		Pembrolizumab monotherapy n/N (%)	Platinum doublet <sup>d</sup> n/N (%)	Absolute difference	HR (95% CI)
KN024 <sup>b</sup>	Progressed	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>
	Median months PFS (range) <sup>c</sup>	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>	<b>██████████</b>
<b>Indirect comparison pembrolizumab combo vs. pembrolizumab monotherapy</b> IPTW weighting only					<b>██████████</b>

<sup>a</sup> Subgroup of patients with PD-L1 Tumour Proportion Score (TPS)  $\geq 50\%$  only

<sup>b</sup> Subgroup of patients with non-squamous histology only

<sup>c</sup> Median for comparator reported for IPTW weighting only

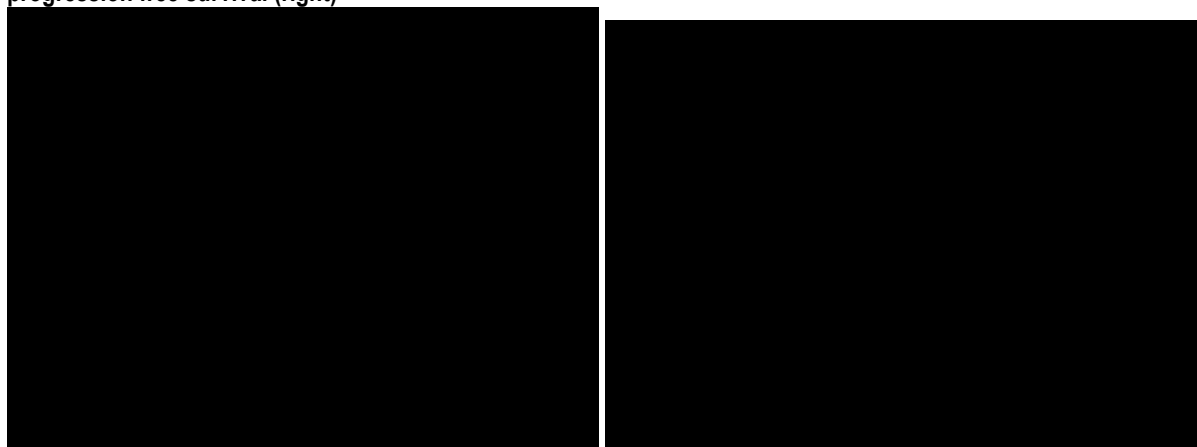
<sup>d</sup> Subgroup of patients treated with cisplatin + pemetrexed or carboplatin + pemetrexed only

Pembro+plat+peme = pembrolizumab+platinum+pemetrexed, PFS = progression free survival; HR = hazard ratio; NR = not reached; CI = confidence interval, IPTW = Inverse Probability of Treatment Weighting,

Figures in bold indicate statistically significant differences

Source: Table 2.6-11, p90 of the submission and Table 13, p28 of Appendix 14 to the submission

Figure 5: Kaplan-Meier curves in KN189 and KN024, ITT population unadjusted – overall survival (left) and progression free survival (right)



Source: Figure 3, p17 and Figure 6, p27 of Appendix 14 to the submission

- 6.17 The information that has been redacted from tables 7 and 8 and figure 5 above shows none of the adjustment methods in the indirect comparison resulted in a HR for OS or PFS that was statistically significantly different between pembrolizumab+platinum+pemetrexed and pembrolizumab. The submission noted that this is likely because the indirect comparison used two subgroups from two trials and was underpowered.
- 6.18 Additionally, the efficacy in the common reference arms (platinum+pemetrexed) of KN189 and KN024 appears to be different, with patients treated with platinum + pemetrexed in KN024 having better OS and PFS outcomes compared to KN189 (longer median OS and PFS, no overlap in OS and PFS Kaplan Meier between 3-15 months).
- 6.19 The PSCR reiterated that the PD-L1 TPS $\geq$ 50% subgroup from KN189 and the non-squamous subgroup from KN024 were not designed to detect differences compared with chemotherapy, and the indirect treatment comparison is not adequately powered to detect a significant difference between pembrolizumab combination therapy and pembrolizumab monotherapy.
- 6.20 The PSCR introduced new evidence from KN042. This study enrolled patients with PD-L1 TPS  $\geq$ 1%. The PSCR re-presented the indirect comparison using the  $\geq$ 50% subgroup from KN042 combined with the patients from KN024. The results of the ITC were little changed, and remained nonsignificant. The PSCR claimed that the similarity of the point estimate, and the narrowing of the confidence intervals provide support for the hypothesis that a statistically significant benefit would be observed if the comparisons were adequately powered.
- 6.21 The ESC suggested that a cost-minimisation approach, based on a claim of non-inferiority, may have been more appropriate for this subgroup (see Economic Analysis).

- 6.22 The PBAC agreed with ESC that the indirect comparison was highly uncertain, and that when the additional toxicity associated with combination therapy is taken into account, pembrolizumab+platinum+pemetrexed may overall be inferior to pembrolizumab monotherapy.
- 6.23 Quality of life data were collected in KN189. Overall, patients treated with pembrolizumab+platinum+pemetrexed reported statistically significantly improved quality of life at Week 21, measured as a least square mean for EORTC QLQ-C30 and EQ-5D VAS, but whether the magnitude of the differences is meaningful is unknown. Quality of life data from KN189 was not directly used in the economic evaluation. Instead, utility values were remapped based on relative time to a patient's death to inform the economic model.

### Comparative harms

- 6.24 Adverse events that occurred at statistically significantly different rates between treatment arms in KN189 are summarised in Table 9.
- 6.25 Overall, the frequency of adverse events (AE) was higher in patients treated with pembrolizumab+platinum+pemetrexed compared to patients treated with platinum doublet but the submission (pp61-62) claims that this was likely due to patients treated with pembrolizumab+platinum+pemetrexed being exposed to the drugs for longer than patients treated with platinum doublet. The dosage regimen in KN189 was consistent with the proposed dosage regimen, therefore it is likely that the increase in AE will be observed in the proposed PBS population. The incidence of adverse events of special interest was also higher in patients treated with pembrolizumab+platinum+pemetrexed compared to platinum doublet, with three patients dying due to Grade 5 pneumonitis in the pembrolizumab+platinum+pemetrexed group.

Table 9: Summary of statistically significant adverse events in KN189

Event	Pembro+plat +peme, n (%) N=405	Platinum doublet, n (%) N=202	OR (95%CI)	RR (95%CI)	RD (95%CI)
≥1 AE	404 (99.8)	200 (99.0)			
Diarrhoea	125 (30.9)	43 (21.3)	<b>1.65 (1.09, 2.52)</b>	<b>1.45 (1.08, 1.97)</b>	<b>0.10 (0.02,0.17)</b>
Rash	82 (20.2)	23 (11.4)	<b>1.98 (1.18, 3.41)</b>	<b>1.78 (1.17, 2.74)</b>	<b>0.09 (0.03, 0.15)</b>
Drug related (DR) AE	372 (91.9)	183 (90.6)	1.17 (0.61,2.19)	1.01 (0.96,1.07)	0.01 (-0.03,0.07)
Diarrhoea	78 (19.3)	22 (10.9)	<b>1.95 (1.16,3.40)</b>	<b>1.77 (1.14,2.75)</b>	<b>0.08 (0.02,0.14)</b>
Febrile neutropenia	24 (5.9)	4 (2.0)	<b>3.12 (1.05,12.52)</b>	<b>2.99 (1.05,8.51)</b>	0.04 (0.00,0.07)
Discontinue due to DR AE	85 (21.0)	17 (8.4)	<b>2.89 (1.64,5.35)</b>	<b>2.49 (1.52,4.08)</b>	<b>0.13 (0.07,0.18)</b>
≥1 AEOSI	92 (22.7)	24 (11.9)	<b>2.18 (1.32,3.71)</b>	<b>1.91 (1.27,2.91)</b>	<b>0.11 (0.04,0.17)</b>
DR AEOSI	75 (18.5)	18 (8.9)	<b>2.32 (1.32,4.26)</b>	<b>2.08 (1.29,3.38)</b>	<b>0.10 (0.04,0.15)</b>
Grade 3-5 AEOSI	36 (8.9)	9 (4.5)	2.09 (0.96,5.04)	<b>2.00 (1.00,4.02)</b>	<b>0.04 (0.00,0.08)</b>
Colitis	9 (2.2)	0 (0.0)	NC	NC	<b>0.02 (0.00,0.04)</b>
Hypothyroidism	27 (6.7)	5 (2.5)	<b>2.81 (1.05,9.49)</b>	<b>2.69 (1.05,6.89)</b>	<b>0.04 (0.00,0.07)</b>

Pembro+plat+peme = pembrolizumab+platinum+pemetrexed, AE = Adverse event, DR = drug related, AEOSI = Adverse events of special

interest, NC = not calculated

Text in bold indicates statistically significant differences

Source: Table 2.5-11, p62, Table 2.5-12, p63, Figure 2.5-5, p64 and Table 2.5-14, p66 and Table 2.5-18, p70 of the submission

### **Benefits/harms**

- 6.26 A summary of the comparative benefits and harms is not provided at this time as the submission did not present the appropriate comparisons to allow this information to be generated.

### **Clinical claim**

- 6.27 The sponsor claimed pembrolizumab+platinum+pemetrexed as superior in terms of effectiveness and inferior in terms of safety compared with platinum+pemetrexed (platinum doublet) followed by PD-(L)1 therapy in patients with PD-L1 TPS <50%.
- 6.28 The submission described pembrolizumab+platinum+pemetrexed as superior in terms of effectiveness and inferior in terms of safety compared with pembrolizumab monotherapy in patients with PD-L1 TPS ≥50%.
- 6.29 For the PD-L1 TPS <50% subgroup, compared with platinum doublet followed by PD-(L)1, the PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data and agreed that the claim of inferior safety was reasonable.
- 6.30 For the PD-L1 TPS ≥50% subgroup, compared with pembrolizumab monotherapy, the PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data and agreed that the claim of inferior safety was reasonable.

### **Economic analysis**

- 6.31 The submission presented a cost-utility partitioned survival analysis based on (i) KN189 subgroup of PD-L1 TPS <50% and (ii) an indirect comparison of KN189 subgroup (PD-L1 TPS ≥50% subgroup) with KN024 (NSQ NSCLC subgroup). A weighted ICER was estimated assuming 71.5% of patients have PD-L1 TPS <50% and 28.5% of patients have PD-L1 TPS ≥50%. This was consistent with the proportional split assumed in the pembrolizumab monotherapy submission.
- 6.32 Table 11 and Table 12 present the summary of the model structure and the utilities used in the economic evaluation presented in the submission, respectively.

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Table 11: Summary of model structure and rationale

Component	Summary	Justification/comments
Time horizon	7.5 years	The PBAC (pembrolizumab monotherapy Nov 2017 PSD, 7.13 p32) has previously accepted a 7.5 year time horizon in first-line NSCLC when particular specifications around costing and extrapolations are applied.
Outcomes	QALY, LYG	Appropriate
Health states	Progression-free, progressed disease, dead	Appropriate.
Methods used to generate results	OS and PFS curves from KN189 (for TPS <50% subgroup) were used to estimate the proportion of patients who are in each health state. For the TPS ≥50% subgroup a constant HR from the indirect comparison of KN189 and KN024 NSQ TPS ≥50% subgroup was applied to the OS and PFS curve for pembrolizumab+platinum+pemetrexed in KN189 to estimate the proportion of patients in each health state for pembrolizumab monotherapy. Extrapolation utilised all the available data and was applied from median OS/PFS onwards. Time on treatment (ToT) curves from KN189 were used to inform the proportion of patients who remain on treatment. The submission assumed that pembrolizumab treatment ceased at 104 weeks. QALY in the model was estimated based on the time before death and unrelated to progression-free or progressed health states. The utility at each time-to-death state was mapped from KN189 (for pembrolizumab+platinum+pemetrexed and platinum doublet) and KN024 (for pembrolizumab monotherapy).	The use of OS and PFS curves to inform partition survival analysis is reasonable. However, the assumption that the HR gradually declined from week 152, reaching a HR=1 at 7.5 years was optimistic. A conservative approach would be to assume that the HR becomes 1 at week 152 (noting that for the ≥50% population, there was no gradual decline in treatment effect, the HR between treatment groups was assumed to be 1 at 90 weeks).  Use of ToT curves rather than remaining on treatment until disease progression was tested in a sensitivity analysis during the evaluation and was shown to have a minimal impact (8.1% increase) on the ICER, thus use of ToT favoured pembrolizumab+platinum+pemetrexed.
Utilities	See Table 12	May not be reasonable and overestimates QALY gain compared to using health state utilities.
Cycle length	1 week	Reasonable

Source: Table 3.1-1, p106 of the submission

Table 12: Time-to-death utilities used in the economic evaluation

PD-L1 TPS <50%			
Time to death (days)	Pembro+plat+peme	Platinum doublet	Pooled treatment <sup>a</sup>
≥360 days	0.764 (0.749, 0.779) n=136	0.774 (0.755, 0.792), n=48	<b>0.767</b> (0.755, 0.779), n=184
Days 180-359	0.702 (0.674, 0.731), n=58	0.699 (0.658, 0.739), n=36	<b>0.701</b> (0.678, 0.724), n=94
Days 30-179	0.620 (0.590, 0.649), n=91	0.656 (0.626, 0.687), n=76	<b>0.637</b> (0.616, 0.659), n=167
<30 days	0.554 (0.411, 0.698), n=19	0.398 (0.220, 0.577), n=13	<b>0.485</b> (0.375, 0.595), n=32
PD-L1 TPS ≥50%			
Time to death (days)	Pembro+plat+peme	Pembrolizumab monotherapy	Pooled treatment
≥360 days	<b>0.767</b> (0.755, 0.779), n=184	<b>0.786</b>	N/A
Days 180-359	<b>0.701</b> (0.678, 0.724), n=94	<b>0.707</b>	
Days 30-179	<b>0.637</b> (0.616, 0.659), n=167	<b>0.600</b>	
<30 days	<b>0.485</b> (0.375, 0.595), n=32	<b>0.562</b>	

Text in bold indicates values used in economic model

<sup>a</sup> applied to both pembrolizumab+platinum+pemetrexed (pembro+plat+peme) and platinum doublet

Source: Table 3.5-1, p141 and 3.5-2, p142 of the submission

6.33 Table 13 summarises the key drivers for the models.

Table 13: Key drivers of the model

Description	Method/Value	Impact on weighted ICER
Assumption of benefit of pembrolizumab+platinum+pemetrexed over pembrolizumab monotherapy	The submission assumed that pembrolizumab+platinum+pemetrexed was more effective than pembrolizumab monotherapy even though this was not supported by the indirect comparison.	High and favours pembrolizumab+platinum+pemetrexed. Assuming no difference in OS and PFS between pembrolizumab+platinum+pemetrexed and pembrolizumab monotherapy results in pembrolizumab+platinum+pemetrexed being dominated, even when weighted.
Assumption of proportional hazards	The OS curves for both comparators are specified by applying hazard ratios to the fitted curves for the pembrolizumab combination arms.	High impact, favours pembrolizumab. Fitting separate curves for the <50% subgroup appears to reduce the OS benefit by around 50%. The model does not permit fitting a separate curve to the pembrolizumab monotherapy arm for the ≥50% subgroup.
Dosage of second-line nivolumab	The submission assumed that patients with PD-L1 TPS <50% will have █ doses of nivolumab at a cost of \$█ after progression when treated with platinum doublet only. ESC has previously (July 2017 pembrolizumab monotherapy PSD) noted that 5.0 doses would be more appropriate.	Moderate and favours pembrolizumab+platinum+pemetrexed. Assuming 5 doses of nivolumab instead of 12 doses in second-line, ICER increased by 20%
Time horizon	Base case time horizon was 7.5 years but given the nature of the disease (Stage IV NSCLC) it might be optimistic	Moderate and favours pembrolizumab+platinum+pemetrexed. Lowering time horizon to 5 years increases ICER by 15.5%

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Description	Method/Value	Impact on weighted ICER
Timing of convergence in OS and PFS HR in platinum doublet in TPS <50%	The submission assumed that the HR between treatment arms in PD-L1 TPS <50% slowly declined from week 152 such that a HR=1.0 occurred only at the end of the model however, in the PD-L1 TPS ≥50% model, a HR=1.0 was applied from week 90. The difference in approaches has not been adequately justified.	Low and favours pembrolizumab+platinum+pemetrexed. Applying HR=1.0 from week 104 (where the submission ceases all pembrolizumab treatment) in TPS <50% increases ICER by 8.1% If survival curves are fitted independently, concerns relating to the application of the HR to survival curves are not relevant.
Function for extrapolation of OS, PFS and ToT	Six different parametric functions were fitted to each of the OS, PFS and ToT curves. Changing the parametric function had variable impact on the ICER.	Variable and can favour both pembrolizumab+platinum+pemetrexed and platinum doublet.

OS = overall survival, PFS = progression free survival, ToT = time on treatment, QALY = quality adjusted life years, ICER = incremental cost effectiveness, PD-L1 = programmed death ligand one, TPS =tumour proportion score.

Source: constructed during evaluation

6.34 The results of the submission’s economic evaluation are presented in Table 14.

**Table 14: Results of the economic evaluations in patients with PD-L1 TPS <50% and TPS ≥50%**

Component	Pembro+plat+peme	Comparator		Increment
		Platinum doublet		
<b>PD-L1 TPS &lt;50%</b>				
Life years gained (LYG)	2.228	1.406		0.821
QALY gained	1.624	0.994		0.630
Cost	\$ [REDACTED]	\$ [REDACTED]		\$ [REDACTED]
Incremental cost per LYG (PD-L1 TPS <50%)				\$ [REDACTED]
Incremental cost per QALY gained (PD-L1 TPS <50%)				\$ [REDACTED]
Component	Pembro+plat+peme	Pembrolizumab mono	Increment	
<b>PD-L1 TPS ≥50%</b>				
Life years gained (LYG)	2.812	2.312	0.501	
QALY gained	2.079	1.721	0.357	
Cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	
Incremental cost per LYG (PD-L1 TPS ≥50%)				\$ [REDACTED]
Incremental cost per QALY gained (PD-L1 TPS ≥50%)				\$ [REDACTED]
<b>Weighted ICER (71.5% TPS &lt;50% and 28.5% TPS ≥50%)<sup>a</sup></b>				
Weighted Incremental cost per LYG				\$ [REDACTED]
Weighted Incremental cost per QALY gained				\$ [REDACTED]

<sup>a</sup> Estimated by 71.5% of ICER from PD-L1 TPS <50% and 28.5% of ICER from PD-L1 TPS ≥50%

Pembro+plat+peme = pembrolizumab+platinum+pemetrexed

Source: Table 3.8-6 and 3.8-7, pp155-156 of the submission

The redacted table shows ICERs in the range of \$15,000 – \$45,000 to \$75,000 – \$105,000 per life year or QALY gained.

6.35 The incremental cost in the submission’s economic model for the PD-L1 TPS <50% subgroup, \$15,000-\$45,000, was markedly higher than in the PD-L1 TPS ≥50%

subgroup, \$15,000 – \$45,000 . This is largely as the drug cost-offsets in the PD-L1 TPS <50% subgroup are based on chemotherapy and a proportion of patients receiving second-line nivolumab, and are far less than the cost-offsets estimated for pembrolizumab monotherapy.

- 6.36 The ICERs for PD-L1 TPS <50% and TPS ≥50% were approximately the same due to the differential effective price for pembrolizumab applied (see Table 2).
- 6.37 The PBAC noted and agreed with the evaluation and ESC concerns regarding the approach taken to the economic model (with the exception that the PBAC agreed it was appropriate to assume a duration of 24 weeks of nivolumab treatment in the second line setting).
- 6.38 However, overall the PBAC did not consider the economic analyses presented by the submission to be informative for decision making given the PBAC’s non-acceptance of the clinical claims on which these analyses were based.

### ***Drug cost/patient***

- 6.39 \$ [REDACTED] over 2 years for all patients in initial submission; \$ [REDACTED] for PD-L1 TPS <50% only patients in pre-PBAC response.
- 6.40 The submission estimated the weighted drug cost per patient from the economic model, assuming 71.5% of PD-L1 TPS <50% (drug cost/patient \$ [REDACTED]) and 28.5% PD-L1 TPS ≥50% (drug cost/patient \$ [REDACTED]), assuming a maximum of 104 weeks (or 35 doses) of treatment. Costs were derived from the economic models and were undiscounted and excluded administration costs. The maximum treatment duration was 2 years for pembrolizumab.
- 6.41 The ESC noted that at the proposed price, the model estimated cost of pembrolizumab in combination treatment in the PD-L1 TPS ≥50% subgroup was considerably higher than the cost of pembrolizumab when used as monotherapy (\$ [REDACTED] versus \$ [REDACTED]).

### ***Estimated PBS usage & financial implications***

- 6.42 This submission was not considered by DUSC. The submission presented an epidemiological approach to estimating the financial impact of listing pembrolizumab+platinum+pemetrexed on the PBS for patients with NSQ, EGFR/ALK negative NSCLC. However market share was partially used to estimate use in patients with PD-L1 TPS ≥50%.
- 6.43 The submission’s estimated financial impact of listing pembrolizumab+platinum+pemetrexed is summarised in Table 16.

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Table 16: Summary of financial estimates in the submission as corrected during evaluation

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Pembro combo patients treated	████	████	████	████	████	████
<b>Number of administrations</b>						
Pembrolizumab 100mg	████	████	████	████	████	████
Pemetrexed 100mg	████	████	████	████	████	████
Carboplatin 150mg <sup>e</sup>	████	████	████	████	████	████
Cisplatin 50mg <sup>e</sup>	████	████	████	████	████	████
<b>Cost of drugs (PBS + RPBS)</b>						
Pembrolizumab 100mg <sup>f</sup>	\$████	\$████	\$████	\$████	\$████	\$████
Pemetrexed 100mg <sup>g</sup>	\$████	\$████	\$████	\$████	\$████	\$████
Carboplatin 150mg <sup>e</sup>	\$████	\$████	\$████	\$████	\$████	\$████
Cisplatin 50mg <sup>e</sup>	\$████	\$████	\$████	\$████	\$████	\$████
Copayments	-\$████	-\$████	-\$████	-\$████	-\$████	-\$████
<b>Total additional drugs net copayment</b>	\$████	\$████	\$████	\$████	\$████	\$████
<b>Reduction in number of patients treated with other drugs</b>						
Platinum doublet <sup>h</sup>	████	████	████	████	████	████
Pembro mono <sup>i</sup>	████	████	████	████	████	████
<b>Reduction in number of administrations for drugs not used</b>						
Pembrolizumab 100mg <sup>ij</sup>	████	████	████	████	████	████
Pemetrexed 100mg	████	████	████	████	████	████
Carboplatin 150mg <sup>e</sup>	████	████	████	████	████	████
Cisplatin 50mg <sup>e</sup>	████	████	████	████	████	████
<b>Reduction in cost of drugs not used (PBS + RPBS)</b>						
Pembrolizumab 100mg <sup>j</sup>	\$████	\$████	\$████	\$████	\$████	\$████
Pemetrexed 100mg <sup>g</sup>	\$████	\$████	\$████	\$████	\$████	\$████
Carboplatin 150mg <sup>e</sup>	\$████	\$████	\$████	\$████	\$████	\$████

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	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Cisplatin 50mg <sup>e</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Copayments</b>	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
<b>Total reduction drugs net copayment</b>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Estimated financial impact for PBS/RPBS</b>						
<b>Total change in PBS/RPBS budget</b>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Estimated financial implications for the health budget</b>						
<b>Change in script numbers<sup>k</sup></b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Total MBS cost<sup>i</sup></b>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Total change in government budget</b>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

1L = first-line treatment

<sup>a</sup> Includes 100 grandfathered patients

<sup>b</sup> 81% of all TPS <50% patients (71.5% of all NSQ NSCLC patients)

<sup>c</sup> 80% of 81% of all TPS ≥50% patients (28.5% of all NSQ NSCLC patients), assume remaining 20% will receive pembrolizumab monotherapy

<sup>d</sup> Estimated by number of patients with PD-L1 TPS <50% multiplied by average number of administrations + number of patients with PD-L1 TPS ≥50% % multiplied by average number of administrations

<sup>e</sup> Assume 72% of all patients will use carboplatin and 28% will use cisplatin

<sup>f</sup> An error was made by the submission; cell referenced to the total pembrolizumab+platinum+pemetrexed cost rather than pembrolizumab only cost, so the submission's estimates were overestimated. Estimates provided in the Commentary are based on an effective weighted price of \$ [REDACTED] (spreadsheet provided with the submission used a cost of \$ [REDACTED], the cost of the whole pembrolizumab+platinum+pemetrexed regimen, not just pembrolizumab)

<sup>g</sup> Values in body of submission (Table 4.3-10, p174) were miscalculated. The submission's spreadsheet had a bad reference for RPBS patients with PD-L1 TPS ≥50% and underestimated the number of administrations for pemetrexed.

<sup>h</sup> Assume 71% of patients with PD-L1 TPS <50% were treated with platinum doublet

<sup>i</sup> Submission *inappropriately* assumed 81% of patients with PD-L1 TPS ≥50% were treated with pembrolizumab monotherapy but did not consider that only 80% switched to pembrolizumab+platinum+pemetrexed. The submission's estimates would have meant that there were MORE patients being substituted for than pembrolizumab+platinum+pemetrexed would have treated.

<sup>j</sup> Refers to pembrolizumab monotherapy, which has a different effective price than pembrolizumab+platinum+pemetrexed

<sup>k</sup> Estimated as total number of administrations for pembrolizumab+platinum+pemetrexed for each drug minus the total number of administrations for drugs not used. The submission (table 4.6-1, p183) included an error as it did not include pemetrexed use in P-L1

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TPS  $\geq$ 50%

<sup>1</sup> submission made two errors in the estimation for MBS costs. Firstly, the item costs were not applied to the number of items before being reported; secondly pembrolizumab monotherapy was not included in the offsets.

Text in italics indicate values calculated during evaluation

Source: constructed during evaluation using 1L NSCLC KN-189 Section 4\_Budget Impact Model\_July 2018.xlsx and section 4 of the submission

*The redacted table shows that at year 6 the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be more than \$100 million per year.*

6.44 There were a number of errors in the financial estimates presented by the submission, all of which have been corrected in the values presented in Table 16:

- The cost of pembrolizumab estimated by the submission was overestimated due to using a cost of \$ [REDACTED], the cost of the whole pembrolizumab+platinum+pemetrexed regimen (not just pembrolizumab) resulting in a double counting of the platinum doublet costs. Estimates provided in above are based on an effective weighted price of \$ [REDACTED];
- The cost of pemetrexed in the submission was underestimated due to RPBS patients in the TPS  $\geq$ 50% being excluded;
- While the submission stated that 80% of those who would have been treated with pembrolizumab monotherapy will switch to pembrolizumab+platinum+pemetrexed, the entire pembrolizumab monotherapy population was accounted for in the cost-offsets provided in the submission. The submission essentially assumed there were more patients treated with pembrolizumab monotherapy while calculating the offsets, than there were treated with pembrolizumab+platinum+pemetrexed; and
- The total number of MBS items presented in the submission were overestimated as the reduction in pembrolizumab monotherapy infusions replaced due to patients being treated with pembrolizumab+platinum+pemetrexed were not accounted for. The number of items above are those accounting for pembrolizumab monotherapy administrations that would no longer occur. Additionally, the submission did not allocate costs to the relevant MBS items, these were included in the estimates above.

6.45 The submission also presented a sensitivity analysis using the ITT population in KN189 instead of separate PD-L1 TPS <50% and  $\geq$ 50% populations, which increased the cost in Year 1 to more than \$100 million (\$60-\$100 million if nivolumab offset was included) to substantially more than \$100 million (more than \$100 million if nivolumab offset was included).

6.46 The ESC considered the submission's estimates of patient numbers to be too high based on the estimates developed during the consideration of the PBS listing for pembrolizumab in 1<sup>st</sup> line NSCLC PD-L1 TPS  $\geq$ 50% population and using the same assumptions to inform the estimates for stage III disease. The ESC proposed the patient numbers in Table 17 as a more reasonable basis for estimating the financial

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impact of listing pembrolizumab for the expanded NSCLC population, however noting that those estimates do not include grandfathered patients.

- 6.47 The pre-PBAC response provided an updated budget impact model for the PD-L1 TPS <50% group only. The sponsor's pre-PBAC estimate is similar to that presented in Table 17. The estimated numbers for the PD-L1 TPS <50% subgroup ranged from [REDACTED] in Year 1 (excluding grandfathering) to [REDACTED] in Year 6 (Table 17). The numbers calculated according to ESC input included an estimate of the number of patients who would progress from Stage III NSCLC to Stage IV and become eligible for pembrolizumab+platinum+pemetrexed.
- 6.48 The pre-PBAC response estimate of the net cost to government for the PD-L1 < 50% subgroup, accounting for the second line offset of nivolumab, was \$30-\$60 million in year 1, increasing to \$60-\$100 million in year 6.
- 6.49 No updated financial estimates for the PD-L1 TPS ≥50% group were included in the pre-PBAC response.
- 6.50 The PBAC noted the high financial cost associated with the sponsor's proposed listing. The PBAC considered the additional costs associated with the listing as presented in the pre-PBAC response appeared implausible as the majority of patients who would be eligible for treatment under the pre-PBAC response's revised proposed listing are already eligible for treatment with a PD-(L)1 inhibitor after platinum doublet therapy. The PBAC requested the sponsor revisit these estimates in any future submission.

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Table 17: Revised Patient Number estimates for pembrolizumab+platinum+pemetrexed, based on ESC advice

PATIENTS DIAGNOSED AT STAGE IV*		2019	2020	2021	2022	2023	2024	
YEAR								
	Agreed 1st line IV Population from pembro 1st line submission PD-L1+, EGFR-, ALK- NSCLC,, all patients	■	■	■	■	■	■	July 2018 PBAC
#1	Total Patients with NSCLC diagnosed at Stage IV EGFR-, ALK- NSCLC	■	■	■	■	■	■	28.5% PDL1+
#2	#1 who are Not ROS-1	■	■	■	■	■	■	1.6% ROS-1
#3	#2 who are NSQ	■	■	■	■	■	■	
#4	#3 who are PD-L1 <50%	■	■	■	■	■	■	74.2% NSQ
#5	#3 who are PD-L1 ≥50%	■	■	■	■	■	■	
	<b>PD-L1 &lt;50%</b>							
#6	Predicted uptake in Pembrolizumab combo for PD-L1<50% (#4*81%)	■	■	■	■	■	■	
	<b>PD-L1 ≥50%</b>							
#7	Predicted uptake in Pembrolizumab combo for PD-L1≥50% (#5 * 81% * 80%)	■	■	■	■	■	■	
#8	Predicted remaining in Pembro mono for PD-L1≥50% (#6 * 81% * 20%)	■	■	■	■	■	■	
#9	Total taking pembro combo (#6 + #7)	■	■	■	■	■	■	
#10	Total taking pembro combo or mono (#6 + #7 + #8)	■	■	■	■	■	■	

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	PATIENTS DIAGNOSED AT STAGE III							
	YEAR	2019	2020	2021	2022	2023	2024	
	Patients with NSCLC diagnosed at Stage III	2,849	2,902	2,956	3,010	3,063	3,117	(AIHW + Mitchell et al (2013)
	Stage III A	1,303	1,327	1,352	1,377	1,401	1,426	11.8%
	Stage III B	1,546	1,575	1,604	1,633	1,662	1,691	14%
#1	Number progressing to Stage IV (= 100% IIIB + 60% IIIA)	2,327	2,371	2,415	2,459	2,503	2,547	assumption
#2	#1 who are Non-Squamous	1,727	1,760	1,792	1,825	1,857	1,890	
#3	#2 who are Performance Status 0-1 at diagnosis	1,093	1,114	1,134	1,155	1,176	1,196	
#4	#3 who are NOT ALK, EGFR or ROS1	859	875	891	907	923	939	
#5	#4 who are PD-L1 <50%	614	625	637	649	660	672	
#6	#4 who are PD-L1 ≥50%	245	249	254	259	263	268	
	<b>PD-L1 &lt;50%</b>							
#7	Predicted uptake in Pembrolizumab combo for PD-L1<50% (#5*81%)							
	<b>PD-L1 ≥50%</b>							
#8	Predicted uptake in Pembrolizumab combo for PD-L1≥50% (#6 * 81% * 80%)							
#9	Predicted remaining in Pembro mono for PD-L1≥50% (#6 * 81% * 20%)							
#10	Total taking pembro combo (#7 + #8)							
#11	Total taking pembro combo or mono (#7 + #8 + #9)							

Source: prepared by Department based on ESC advice.

<b>Grand Total taking pembro combo (stage IV #10 + stage III #10)</b>								
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### **Quality Use of Medicines**

- 6.51 The sponsor indicated it will develop materials to provide the latest information to health care practitioners on how to identify and manage treatment-related adverse events. Additionally, educational activities (e.g. workshop sessions and conferences) have been planned to disseminate new information and incorporate peers as teachers. A 1-800 medical information service run by the sponsor is also available to address queries.

### **Financial Management – Risk Sharing Arrangements**

- 6.52 The sponsor indicated its willingness to enter into a risk sharing arrangement which includes a special pricing arrangement (SPA) and annual subsidy caps, but details on the subsidy caps were not provided.
- 6.53 The PBAC noted that the listing of pembrolizumab as requested will have implications for existing RSAs for the use of PD-(L)1 therapies for NSCLC.

*For more information on PBAC's view, see Section 7; PBAC Outcome*

## **7 PBAC OUTCOME**

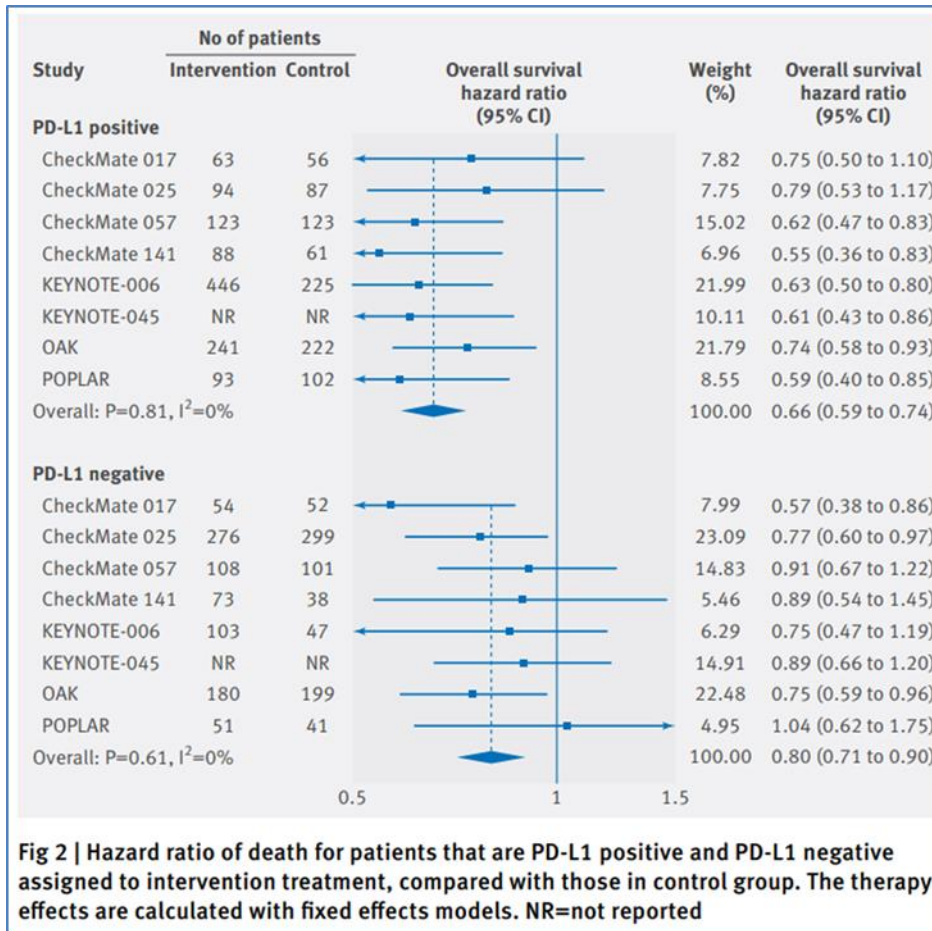
- 7.1 The PBAC did not recommend listing of pembrolizumab for the first line treatment of Stage IV NSCLC in combination with pemetrexed and platinum chemotherapy, on the basis that, in patients with a programmed death ligand 1(PD-L1) tumour proportion score (TPS)  $\geq 50\%$  the available evidence does not support there being an additional benefit, in terms of efficacy, for combination treatment over pembrolizumab monotherapy and because the safety of combination treatment appears worse than monotherapy treatment in this patient group. In patients with a PD-L1 TPS  $< 50\%$  there is uncertainty in the magnitude of the incremental benefit, if any, over the alternative therapy of chemotherapy followed by a PD-(L)1 inhibitor.
- 7.2 Furthermore, the PBAC formed the view, based on the totality of the evidence now available, that PD-L1 expression status alone is insufficient in determining which patients with NSCLC should be offered PD-(L)1 inhibitor therapy (see Figure 6<sup>3</sup>). The PBAC considered that a listing that made pembrolizumab available to patients as a first-line treatment for Stage IV NSCLC irrespective of PD-(L)1 status was appropriate but noted that this would require a reduction in the proposed price. The PBAC also noted the high estimated cost of subsidising pembrolizumab in this setting at the

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<sup>3</sup> Shen, Xian & Zhao, Bin. (2018). Efficacy of PD-1 or PD-L1 inhibitors and PD-L1 expression status in cancer: Meta-analysis. *BMJ*. 362. k3529. 10.1136/bmj.k3529.

proposed price.

**Figure 6: Hazard ratio of death for patients that are PD-L1 positive and negative in various trials compared with control group (taken from Shen et al)**



- 7.3 The PBAC noted the sponsor’s request in its pre-PBAC response that the PBAC defer consideration of the listing request for the PD-L1 TPS ≥50% subgroup. The PBAC did not agree to this request on the grounds that the PBAC considered all patients (irrespective of their tumour PDL1 status) should have the choice, based on the advice of their clinician, to undertake treatment with pembrolizumab in combination with chemotherapy.
- 7.4 The PBAC considered that the proposed restriction wording was appropriate, although agreed with the ESC that the effectiveness of pembrolizumab in patients with ROS1 translocations is unknown and the restriction should preclude the use of pembrolizumab in this subset.
- 7.5 The PBAC noted the lack of evidence for the effectiveness of sequential use of PD-(L)1 therapies, and recommended that the restriction preclude the use of pembrolizumab+platinum+pemetrexed in patients previously treated for NSCLC with

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PD-(L)1 therapies, regardless of disease stage or treatment line.

- 7.6 The PBAC noted that the submission divided the target patient population into patients with a PD-L1 TPS < 50% and patients with a PD-L1 TPS ≥50%, with different proposed comparators and clinical and economic analyses. Although the PBAC acknowledged the submission's approach is aligned with the current PBS availability of pembrolizumab monotherapy for patients with a PD-L1 TPS ≥50%, the PBAC did not consider the submission's nominated comparators to be appropriate. The PBAC considered that sequential treatment with a platinum doublet followed by PD-(L)1 therapy, or PD-(L)1 therapy followed by platinum doublet to be the appropriate comparators in these settings, respectively.
- 7.7 The PBAC noted that the KN-189 clinical trial demonstrated a statistically significant improvement in overall and progression free survival for the ITT and PD-L1 TPS <50% and ≥50% populations treated with pembrolizumab+platinum+pemetrexed compared with platinum doublet. However the data from this trial are immature, with median overall survival not yet reached in the pembrolizumab+platinum+pemetrexed arm.
- 7.8 For the PD-L1 TPS ≥50% subgroup, the PBAC agreed with ESC that the indirect comparison with pembrolizumab monotherapy using the KN024 trial was highly uncertain. The PBAC considered that the transitivity of the studies had not been adequately addressed. The PBAC considered that an indirect comparison relying upon subgroups from each trial was inherently uncertain. The PBAC noted that the estimate of the indirect treatment effect was not statistically significant, and a claim of non-inferiority would have been more appropriate.
- 7.9 PBAC considered that for the TPS ≥50% subgroup pembrolizumab+platinum+pemetrexed could not be considered superior to pembrolizumab monotherapy in terms of effectiveness and was likely inferior in terms of adverse effects. For the TPS <50% subgroup, it was uncertain whether the combination of pembrolizumab with doublet chemotherapy conferred an advantage over sequential use chemotherapy followed by pembrolizumab (or other PD1/PD-(L)1 inhibitors).
- 7.10 Regarding the economic analysis for the PD-L1 TPS <50% subgroup, the PBAC agreed with the ESC that the extrapolation method, which applied a constant hazard ratio to the treatment effect until week 152, based on trial data with a maximum follow up of less than 2 years, and a median follow up of less than one year, was uncertain. The PBAC noted that the assumed hazard ratio from week 152 until the end of the modelled time horizon of 7.5 years remained less than one (favourable to pembrolizumab+platinum+pemetrexed). The PBAC considered that this approach was not conservative and likely underestimated the ICER.
- 7.11 The PBAC agreed with the ESC that separately fitting OS extrapolations may be more appropriate, but considered that any extrapolation out to 7.5 years that maintained a

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substantial separation of the survival curves to be uncertain in the context of the maturity of the trial data.

- 7.12 The PBAC noted that, if the subsequent use of PD-(L)1 inhibitors in the key trial differed from use in the Australian setting, then the treatment effect observed in the key trial may also differ in Australian practice, and this will affect the estimate of the ICER. The PBAC noted that the proportion of patients in KN-189 who crossed over was reported for the ITT population, but could not be located for the PD-L1 TPS <50% subgroup.
- 7.13 The PBAC noted that the economic analysis for the PD-L1 TPS <50% subgroup was sensitive to the choice of extrapolation function and to the extent of cost-offsets from second-line treatment with PD-(L)1 therapies, and considered that both of these estimates were uncertain.
- 7.14 Based on the immaturity of the data and the uncertainty regarding the comparability of subsequent use of PD-(L)1 inhibitors in KN-189 in the PD-L1 TPS <50% subgroup and in the Australian setting, the PBAC considered a more appropriate approach may be to allow pembrolizumab use in this setting at a price/cost that is aligned to the cost of second line PD-(L)1 inhibitors.
- 7.15 Regarding the economic analysis for the PD-L1 TPS ≥50% group, the PBAC considered a cost-utility analysis inappropriate in the context of a highly uncertain indirect comparison, based on subgroups with questionable transitivity, and with no significant difference in treatment effect between pembrolizumab monotherapy and pembrolizumab+platinum+pemetrexed. Applying a cost utility approach, and modelling no difference in treatment effect, the resulting ICER is dominated due to the inferior safety profile of pembrolizumab+platinum+pemetrexed.
- 7.16 The PBAC agreed with ESC that a cost-minimisation approach would be more appropriate for this patient group.
- 7.17 The PBAC also noted that the newly available evidence from KN042 which involved 599 patients with PD-L1 TPS ≥50% (receiving either pembrolizumab monotherapy or chemotherapy), while still showing pembrolizumab treatment to result in significantly better overall survival than chemotherapy, appeared to show a lower absolute incremental benefit than in KN024. The PBAC noted the arguments put forward by MSD in its 1 October 2018 response to a request from the Department for further information and an updated economic model for pembrolizumab monotherapy... incorporating the results from KN042. . The PBAC further noted that in its pre-PBAC response, MSD acknowledged that that new economic analyses are relevant to the KN024 value proposition but does not currently have access to a KN042 economic model to submit at this time.
- 7.18 The PBAC agreed that it is important for the economic model submitted with the

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July 2018 submission for pembrolizumab monotherapy for NSCLC to be re-run incorporating the results from KN042, to determine if these results have an impact on the value proposition put to the PBAC in July 2018 and upon which the value proposition for the PD-L1  $\geq 50\%$  subgroup in the current submission is based.

- 7.19 The PBAC noted the high financial cost associated with the sponsor's proposed listing. The PBAC considered the additional costs associated with the listing as presented in the pre-PBAC response appeared implausible as the majority of patients who would be eligible for treatment under the proposed listing are already eligible for treatment with a PD-(L)1 inhibitor before or after platinum doublet therapy. The PBAC requested the sponsor revisit these estimates in any future submission.
- 7.20 The PBAC advised the Minister examine the potential for a broad PBS subsidy listing for PD-(L)1 inhibitors for NSCLC, as substantial evidence and experience is now available for four PD-(L)1 medicines in this setting. The PBAC considered there is potential for a NSCLC listing that allows patients of WHO performance status 0 and 1 access to a single course of treatment with a PD-(L)1 inhibitor, irrespective of disease stage (unresectable stage III or IV), biomarker status, line of treatment (adjuvant, 1<sup>st</sup> or later line), and with or without concomitant cytotoxic therapy. This would allow the decision regarding timing the PD-(L)1 inhibitor to be determined by the clinician and patient. The PBAC noted a lack of robust evidence to support the efficacy of sequential courses of PD-(L)1 checkpoint inhibitors and considered limiting treatment with a PD-(L)1 to once per lifetime appropriate at this time.
- 7.21 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**

MSD is disappointed with this outcome and hopes to work with the government to achieve an evidence-based first line solution for all NSCLC patients without a targetable mutation as soon as possible. MSD further notes that the assessment of safety undertaken by the PBAC was based on a naïve comparison of adverse event rates undertaken during the evaluation.