

**7.09 PEMBROLIZUMAB,  
Solution concentrate for I.V. infusion 100 mg in 4 mL,  
Keytruda<sup>®</sup>,  
Merck Sharp & Dohme (Australia) Pty Ltd.**

**1 Purpose of Application**

- 1.1 The resubmission requested a Section 100 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). The requested listing was for the treatment of patients with Stage IV non-squamous (NSQ) non-small cell lung cancer (NSCLC), who are epidermal growth factor receptor (EGFR) wild type, negative for anaplastic lymphoma kinase (ALK) or c-ROS proto-oncogene (ROS1) gene rearrangement, and with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- 1.2 This was the second submission to request to list pembrolizumab+platinum+pemetrexed for this indication, with the first submission considered by PBAC in November 2018. Currently pembrolizumab is subsidised for use as monotherapy in patients with Stage IV NSCLC, who are EGFR wild type and ALK translocation negative, have a World Health Organisation (WHO) status of 0 or 1 AND have a programmed death ligand 1(PD-L1) tumour proportion score (TPS)  $\geq 50\%$  (both NSQ and squamous (SQ)).
- 1.3 The requested basis for listing in the resubmission were cost-effectiveness analyses of pembrolizumab+platinum+pemetrexed compared with two comparators, which differed depending on the patient's PD-L1 TPS status ( $< 50\%$  or  $\geq 50\%$ ) (Table 1).

**Table 1: Key components of the clinical issue addressed by the resubmission**

Component	Description
Population	Previously untreated patients with Stage IV non-small cell lung cancer whose tumours are non-squamous and are EGFR wild-type, <u>ROS-1 negative</u> and ALK translocation negative and whose ECOG status is 0 or 1.
Intervention	Pembrolizumab + platinum chemotherapy + pemetrexed <u>followed by single-agent chemotherapy</u>
Comparator	For patients with PD-L1 TPS $< 50\%$ : platinum doublet <u>followed by a PD-(L)1 inhibitor</u> For patients with PD-L1 TPS $\geq 50\%$ : pembrolizumab monotherapy <u>followed by platinum doublet</u>
Outcomes	OS and PFS
Clinical claim	In TPS $< 50\%$ : Pembrolizumab + platinum + pemetrexed (followed by single-agent chemotherapy) is superior in terms of efficacy and inferior but manageable in terms of safety to platinum + pemetrexed (followed by a PD-(L)1 inhibitor)

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	In TPS ≥50%: Pembrolizumab + platinum + pemetrexed (followed by single agent chemotherapy) is superior in terms of efficacy and inferior in terms of safety to pembrolizumab monotherapy followed by platinum doublet.
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The underlined wording is the addition in the resubmission compared with the previous submission.

NSQ = non-squamous, NSCLC = non-small cell lung cancer, EGFR = epidermal growth factor receptor, ALK = anaplastic lymphoma kinase, ECOG = Eastern Cooperative Oncology Group, 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.

Source: Table 1.1-2, p15 of the resubmission

## 2 Requested listing

2.1 The abridged restriction criteria are provided below with Secretariat additions in italics and deletions in strikethrough.

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount (published)	Proprietary name and manufacturer
Pembrolizumab 100 mg injections	200 mg	3 (initial) 6 (continuing/grandfathering)	\$9,186.18 private price \$9,023.22 public price	Keytruda®, Merck Sharp & Dohme (Australia) Pty Ltd

<b>Category/program</b>	Chemotherapy Items for Private Hospital Use, Chemotherapy items for Public Hospital use.
<b>Severity:</b>	Stage IV (metastatic)
<b>Condition:</b>	<del>Non-squamous</del> non-small cell lung cancer
<b>PBS Indication:</b>	Stage IV (metastatic) <del>non-squamous</del> non-small cell lung cancer
<b>Treatment phase:</b> (initial)	Initial ( <del>combination platinum+pemetrexed+pembrolizumab</del> )
<b>Treatment phase:</b> (continuing)	Continuing <del>combination (pemetrexed+pembrolizumab)</del>
<b>Treatment phase:</b> (grandfathering)	Grandfathering <del>pembrolizumab in combination with cisplatin or carboplatin and pemetrexed or in combination with pemetrexed alone</del>
<b>Restriction:</b> <b>Section 100 (HSD)</b> <b>Authority required (STREAMLINED)</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> (initial)	<p>The patient must not have received prior systemic treatment for this condition in the metastatic setting</p> <p>AND The condition must be non-squamous type non-small cell lung cancer</p> <p>AND The treatment must be in combination with pemetrexed</p> <p>AND the treatment must be in combination with carboplatin OR the treatment must be in combination with cisplatin</p> <p>AND Patient must have a WHO performance status score of 0 or 1,</p> <p>AND</p> <p><i>The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement or a c-ROS proto-oncogene 1 (ROS1) gene rearrangement in tumour material</i></p> <p><del>AND The treatment with pembrolizumab must not exceed a total of 6 doses at a dose of 200 mg every 3 weeks.</del></p>

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	<del>AND The patient may only receive one course of anti-PD-(L)1 treatment in their lifetime for this condition</del>
<b>Clinical criteria:</b> (continuing)	<p><del>Patient must have previously been issued with an Authority prescription for this indication</del>  <del>Patient must have previously received PBS-subsidised treatment with this drug for this condition</del>  AND  <del>Patient must not have progressive disease;</del>  <del>Patient must not have developed disease progression while being treated with this drug for this condition</del>  AND  AND The treatment must be in combination with pemetrexed  <del>AND The treatment with pembrolizumab must not exceed a total of 6 doses at a maximum dose of 200 mg every 3 weeks</del>  <del>AND Treatment must not exceed 35 administrations or 2 years of continuous treatment overall (initial + continuing treatment).</del></p>
<b>Clinical criteria:</b> (grandfathering)	<p><del>Patient must have stable or responding disease;</del>  <del>Patient must not have developed disease progression while being treated with this drug for this condition</del>  AND Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to (date of listing),  AND Patient must have had a WHO performance status of 0 or 1 at the time of treatment initiation,  <del>AND The patient may only receive one course of anti-PD-(L)1 treatment in their lifetime for this condition</del></p>
<b>Population criteria:</b>	<del>Patient must have no evidence of an activating epidermal growth factor gene or of an anaplastic lymphoma kinase (ALK) gene rearrangement or of c-ROS proto-oncogene 1 (ROS1) gene rearrangement in tumour material</del>
<b>Administrative Advice</b>	<p>No increase in the maximum number of repeats will be authorised.  In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.  Special pricing arrangement apply</p>

2.2 As in the previous submission, a special pricing arrangement (SPA) was proposed. The proposed effective price of pembrolizumab when used in combination with platinum and pemetrexed was weighted by the proportion of use in patients with PD-L1 TPS status ( $\geq 50\%$  and  $< 50\%$ ). The effective prices proposed in the resubmission are summarised in Table 2. The PSCR proposed a revised price for the TPS  $\geq 50\%$  population of \$ [REDACTED] per 100 mg vial.

**Table 2: Proposed effective price for pembrolizumab when used in combination with platinum chemotherapy and pemetrexed**

	Effective AEMP per 100mg vial	Weighting <sup>b</sup>
<b>Current resubmission</b>		
PD-L1 TPS <50%	\$ [REDACTED]	86.5%
PD-L1 TPS ≥50% <sup>a</sup>	\$ [REDACTED]	13.5%
Weighted	\$ [REDACTED]	-
<b>Pre-Sub-Committee Response</b>		
PD-L1 TPS <50%	\$ [REDACTED]	86.5%
PD-L1 TPS ≥50%	\$ [REDACTED]	13.5%
Weighted	\$ [REDACTED]	-
<b>November 2018 submission</b>		
PD-L1 TPS <50%	\$ [REDACTED]	71.5%
PD-L1 TPS ≥50%	\$ [REDACTED]	28.5%
Weighted	\$ [REDACTED]	-

Shaded cells previously considered by PBAC

PD-L1 = programmed cell death ligand 1; TPS = tumour proportion score.

<sup>a</sup> This price is the same as the current price for pembrolizumab as monotherapy in this patient population (not the 6% price reduction to \$ [REDACTED] per 100 mg, recommended at the March 2019 PBAC meeting).

<sup>b</sup> For the current resubmission, this weighting was based on a ratio of the expected utilisation of vials between the populations. For the previous submission, this weighting was based on a screening prevalence from KN024 (28.5% TPS≥50%).

Source: Compiled during the evaluation. Current estimates from 'Pembrolizumab\_1L NSCLC KN0189\_Budget Impact Model\_March 2019.xlsx

- 2.3 The resubmission proposed a lower price for pembrolizumab when used in combination with platinum+pemetrexed compared with that proposed in the previous submission. In addition, the vial price proposed in the resubmission and the PSCR for the TPS ≥50% population is lower than that proposed for the TPS <50% population (Table 2).
- 2.4 When the PBAC considered the value proposition of pembrolizumab monotherapy in March 2019, taking into account the hazard ratios of pembrolizumab versus standard of care observed in both KN024 and KN042 trials, the PBAC noted that the ex-manufacturer price of pembrolizumab should be reduced to \$ [REDACTED] per 100 mg vial to achieve an ICER of \$45,000/QALY - \$75,000/QALY. The ESC noted that the price offered in the PSCR for the TPS ≥50% population (\$ [REDACTED] per 100 mg vial) was lower than the price recommended for pembrolizumab monotherapy at the March 2019 PBAC.
- 2.5 The resubmission considered that pembrolizumab+platinum+pemetrexed would be used instead of pembrolizumab monotherapy in patients with aggressive disease and a high tumour burden. However, this was not specifically reflected in the requested restriction.

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

### 3 Background

#### Registration status

3.1 Pembrolizumab was approved by the TGA on 12 June 2018, for use in combination with pemetrexed + platinum chemotherapy, for the first-line treatment of patients with metastatic, non-squamous NSCLC and the indication was updated on 5 December 2018, for use only in patients “with no EGFR or ALK genomic tumour aberrations”.

#### Previous PBAC consideration

3.2 Table 3 summarises the outstanding PBAC concerns and how the resubmission addressed these.

**Table 3: Key outstanding matters from previous PBAC consideration (November 2018 PBAC Meeting) and how the resubmission addressed these**

Paragraph: November 2018 PBAC PSD	How the resubmission addressed the issue
7.2: The PBAC considered that a listing that made pembrolizumab available to patients as a first-line treatment for Stage IV NSCLC, irrespective of PD-L1 status, was appropriate but that this would require a reduction in the proposed price. 7.3: The PBAC did not agree to the request by the sponsor in the pre-PBAC response to defer consideration in patients with TPS ≥50%. The PBAC considered all patients (irrespective of their tumour PD-L1 status) should have the choice, based on the advice of their clinician, to undertake treatment with pembrolizumab in combination with chemotherapy.	Accepted by sponsor. Restriction does not include criteria based on PD-L1 status. The price for the PD-L1 TPS ≥50% population was aligned to the current price for pembrolizumab monotherapy, (not the █% price reduction recommended at the March 2019 PBAC meeting). The PSCR proposed a price for the TPS ≥50% population, which was lower than the price recommended for this population at the March 2019 PBAC.
7.4: The PBAC considered the effectiveness of pembrolizumab in patients with ROS-1 translocations is unknown and the restriction should preclude the use of pembrolizumab in this subset	Accepted by sponsor. ROS-1 patients have been excluded in the requested restriction in the resubmission.
7.5: The PBAC recommended that the restriction preclude the use of pembrolizumab+platinum+pemetrexed in patients previously treated for NSCLC with PD-(L)1 therapies, regardless of disease stage or treatment line.	Accepted by sponsor. The proposed restriction allows use of PD-(L)1 inhibitors only once per lifetime for NSCLC.
7.6: For patients with a PD-L1 TPS <50% and patients with a PD-L1 TPS ≥50%, the PBAC did not consider the submission’s nominated comparators to be appropriate, and 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.	Accepted by sponsor. The sponsor has updated the comparators as follows: TPS <50%: Platinum doublet chemotherapy followed by PD-(L)1 inhibitors. TPS ≥50%: Pembrolizumab monotherapy followed by platinum doublet.

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Paragraph: November 2018 PBAC PSD	How the resubmission addressed the issue
7.7: The PBAC noted that the KN-189 clinical trial demonstrated a statistically significant improvement in OS and PFS in the ITT, TPS <50% and ≥50% populations treated with pembrolizumab+platinum+pemetrexed. However, the data remained immature with median OS not reached in the pembrolizumab+platinum+pemetrexed arm.	The sponsor provided an additional 6 months' follow up data from KN189. For the ITT population, median OS has now been reached in both trial arms (pembrolizumab+platinum+pemetrexed: 22.0 months, 95% CI: 19.5, 25.2; Standard of Care (SoC) 11.3 months, 95% CI: 8.7, 15.1). In the updated data, the median OS for patients with a PD-L1 TPS ≥50% was not reached.
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 noted that the estimate of the indirect treatment effect was not statistically significant, and a claim of non-inferiority would have been more appropriate.	The estimate of PFS HR for the indirect comparison between KN189 and (KN024+KN042) was statistically significant (PFS HR: [redacted] (95% CI: [redacted], [redacted])), but the OS HR was not (OS HR: [redacted] (95% CI: [redacted], [redacted])). There were important transitivity and methodological concerns with the indirect comparisons.
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 KN189 who crossed over was reported for the ITT population, but could not be located for the PD-L1 TPS <50% subgroup.	The resubmission provided data on subsequent therapies which indicated that, for the TPS <50% population, 88% of patients who took a 2 <sup>nd</sup> line treatment went on to receive an anti-PD-(L)1. The resubmission stated that this was aligned with the current usage of 2 <sup>nd</sup> line PD-(L)1-inhibitor therapy after failure of chemotherapy in the Australian setting (92%). "Taken together, this supports a significant clinical benefit of Pembro Combo compared to platinum doublet followed by an anti-PD-(L)1 which is applicable to the Australian setting."
7.10: Regarding the economic analysis for the PD-L1 TPS <50% subgroup, the PBAC agreed with the ESC that the extrapolation method, 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 substantial separation of the survival curves to be uncertain in the context of the maturity of the trial data.	The base case CUA for the PD-L1 <50% population employed the most conservative extrapolation function available (i.e. Gompertz) fitted individually to the pembrolizumab+platinum+pemetrexed and platinum doublet OS functions instead of employing a proportional hazards approach. These survival curves converge by the end of the modelled time horizon (i.e. 7.5 years).  The use of the better fitting Weibull function was also tested in sensitivity analyses. This generated a lower ICER than that for the base case.
7.16: The PBAC agreed with ESC that a cost-minimisation approach would be more appropriate for this patient group [TPS ≥50% subgroup]	The resubmission disagreed with the PBAC and again presented a CUA for this patient group. The PSCR offered a price reduction for this population.
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.	The resubmission provided updated financial estimates based on the parameters identified in the PBAC Minutes, with the exception of the uptake of current chemotherapy regimens for the PD-L1 TPS <50% population (adjusted from 81% to 71%) and market share of pembrolizumab+platinum+pemetrexed relative to pembrolizumab monotherapy (from 80% to 30%).

CUA = cost utility analysis; ITC = indirect treatment comparison; NSQ = non-squamous; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1, TPS = tumour proportion score, OS = overall survival, PFS = progression free survival HR = hazard ratio; ITT = intention to treat.

Source: November 2018 PBAC PSD and Section 1 of the resubmission

## 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).
- 4.2 Pembrolizumab+platinum+pemetrexed was proposed as first-line treatment for patients with Stage IV NSQ NSCLC, with an ECOG status of 0 or 1, who are EGFR wild type and negative for ALK or ROS1 gene rearrangements in tumour material. This is unchanged from the previous submission, except for the explicit preclusion of patients with ROS1 gene rearrangement, which is in line with PBAC advice on the previous submission.

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

## 5 Comparator

- 5.1 The resubmission nominated two comparators:
- PD-L1 TPS <50%: platinum doublet followed by a PD-(L)1 inhibitor;
  - PD-L1 TPS ≥50%: pembrolizumab monotherapy followed by a platinum doublet.
- 5.2 Compared with the previous submission, the nominated comparators in the resubmission have been revised to include sequential treatment. This includes a platinum doublet followed by PD-(L)1 therapy, or PD-(L)1 therapy followed by platinum doublet for patients with PD-L1 TPS <50% and PD-L1 TPS ≥50%, respectively. These changes are appropriate and consistent with PBAC advice on the previous submission (Paragraph 7.6, Item 6.6, Pembrolizumab PSD, November 2018).
- 5.3 The resubmission also identified atezolizumab+bevacizumab+carboplatin+paclitaxel (ABCP) as a near-term comparator, which was appropriate as it was recommended for a similar population at the March 2019 meeting.

*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 clinical case studies, and discussed how the drug would be used in practice. The PBAC considered that the hearing was not informative as it did not add substantively to the evidence presented in the submission.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (2) and health care professionals (16) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with pembrolizumab in combination with chemotherapy, including survival benefits and tolerable side effects when compared with chemotherapy alone. Several comments supported the listing, as it would provide access to first-line pembrolizumab for patients with lower PD-L1 expression.
- 6.3 The PBAC also noted and welcomed input from the Lung Foundation Australia. The Lung Foundation considered that this regime would be offered as routine standard of care for patients for patients with Stage IV non-squamous NSCLC, as it extends both PFS and OS, and would make first-line immunotherapy available to patients regardless of PD-L1 expression. The Lung Foundation commented that a proportion of patients with TPS<50% who progress after chemotherapy do not currently go on to receive available second line immunotherapy agents. Furthermore, for patients with TPS>50%, potentially eligible patients may be unable to access pembrolizumab monotherapy if a biopsy is unsuitable for testing and therefore their PD-L1 status unknown. Thus, it claimed that the current PBS arrangements do not provide the maximum possible impact of immunotherapy for the maximum number of NSCLC patients.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the Keynote-189 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab and chemotherapy combination therapy, of 5 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>a</sup> based on a comparison with chemotherapy alone.

### **Clinical trials**

- 6.5 The resubmission was based on:

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<sup>a</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

- In patients with PD-L1 TPS <50%, a subgroup analysis of TPS <50% patients from one head-to-head randomised trial (KN189), comparing pembrolizumab+platinum+pemetrexed versus platinum+pemetrexed, followed by anti PD-(L)1 therapy (patients enrolled in KN189 were not selected based on PD-L1 status). This was unchanged from the previous submission. Updated efficacy data from the previous submission from KN189 (median duration of follow-up 18.7 months vs. 10.5 months in the previous submission) were provided in the resubmission.
- In patients with PD-L1 TPS ≥50%, an indirect comparison between pembrolizumab+platinum+pemetrexed (KN189) and pembrolizumab monotherapy (KN024: ITT PD-L1 TPS ≥50%; KN042: ITT PD-L1 TPS ≥1%), via platinum doublet as a common reference. These indirect comparisons involved the use of multiple subgroups and exclusions from the included studies to enable a comparison based on patients similar in terms of PD-L1 TPS status (≥50%) and platinum doublet received (platinum+pemetrexed). The PD-L1 TPS ≥50% patient population was a subgroup from the KN189 and KN042 studies, and the ITT from the KN024 study (Table 4). The indirect comparison of pembrolizumab+platinum+pemetrexed with pembrolizumab monotherapy in the previous submission was based on the KN189 and KN024 studies, with data from Study KN042 provided in the PSCR. The results of KN024 and KN042 were discussed at the March 2019 PBAC meeting in the context of the value of the pembrolizumab monotherapy listing (Agenda Item 3.01).
- A naïve indirect comparison between pembrolizumab+platinum+pemetrexed and ABCP, as a near-term comparator, was also presented in the resubmission.
- A summary of the treatment arms and population characteristics selected for the indirect comparison is presented in Table 4.

**Table 4: Summary of treatment arms and population selected for the indirect comparison**

Study	Treatment arms	Population Selection
KN189	- Pembrolizumab + Chemotherapy <sup>a</sup> - Chemotherapy <sup>a</sup>	Strong PD-L1 subjects (TPS ≥50%) <sup>b</sup>
KN042	- Pembrolizumab - Chemotherapy <sup>a</sup>	Non-squamous histology subjects <sup>c</sup> Strong PD-L1 subjects (TPS ≥50%) <sup>b</sup>
KN024	- Pembrolizumab - Chemotherapy <sup>a</sup>	Non-squamous histology subjects <sup>c</sup>

<sup>a</sup> Pemetrexed and carboplatin or pemetrexed and cisplatin for KN189 and KN024 and pemetrexed and carboplatin for KN042

<sup>b</sup> KN024 contains TPS ≥50% subjects only; patients with the same criterion are selected from KN189 and KN042

<sup>c</sup> KN189 contains non-squamous subjects only; patients with the same criterion are selected from KN042 and KN024

Source: Table 2.6.10, p85 of the resubmission

6.6 Details of the trials presented in the resubmission are provided in Table 5.

**Table 5: Trials and associated reports presented in the resubmission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Pembrolizumab + platinum + pemetrexed versus platinum doublet</b>		
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) <sup>a</sup> Gandhi et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer.	March 2018  <i>N Engl J Med</i> 2018; 378(22): 2078-2092
<b>Pembro Mono versus platinum doublet (used for indirect comparison of Pembro Combo from KN189 with Pembro Mono)</b>		
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. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. Reck et al. Updated Analysis of KEYNOTE-024 Pembrolizumab versus platinum-based chemotherapy for advanced non-small cell lung cancer with PD-L1 TPS of 50% or greater.	11 July 2016  <i>N Engl J Med</i> 2016; 375(19):1823-1833Epub 2016 Oct 8 <i>J Clin Oncol</i> 2019; 37(7):537-546
KN042	A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) Versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (KEYNOTE-042) Lopes et al, 2018, Pembrolizumab vs Platinum-Based Chemotherapy as a first line therapy for advanced/metastatic NSCLC with a TPS ≥1%. Mok et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial.	December 2018  <i>Presentation at American Society of Clinical Oncology Annual Meeting, Jun 2018</i>  <i>Lancet</i> 2019; 393(10183): 1819-1830 <sup>b</sup>

Pembro Combo = pembrolizumab+platinum+pemetrexed followed by single agent chemotherapy (e.g. docetaxel); Pembro Mono = pembrolizumab monotherapy followed by platinum doublet; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1, TPS = tumour proportion score.

<sup>a</sup> Data from September 2018 cut off provided as tables in Attachments

<sup>b</sup>Published 4 April 2019 (post submission)

Source: Table 2.2-1, pp42-3 of the resubmission

6.7 The key features of the included trials are summarised in Table 6.

Table 6: 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+pemetrexed (TPS &lt;50% subgroup)</b>						
KN189	376 (ITT 616)	R, DB Median 16.7 mths <sup>f</sup> (Median 10.5 mths in the previous submission)	Low, planned subgroup analysis	Untreated (first-line) NSQ Stage IV 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+pemetrexed						
KN189	202 <sup>a</sup> (ITT 616)	R, DB Median 16.7 mths <sup>f</sup> (Median 10.5 mths in the previous submission)	Low, planned subgroup analysis	Untreated (first-line) NSQ Stage IV 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+pemetrexed						
KN024 <sup>c</sup>	199 (ITT 305)	R, OL Median 11.2 mths	Low <sup>b</sup> ; OS is objective outcome High risk of bias for indirect comparison	Untreated (first-line) NSQ Stage IV 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
KN042 <sup>d</sup>	599 <sup>e</sup> (ITT 1,274)	R, OL Median 14.0 mths	Low <sup>b</sup> ; OS is objective outcome High risk of bias for indirect comparison	Untreated (first-line) NSQ Stage IV NSCLC, EGFR and ALK negative, ECOG 0 or 1 and TPS ≥50%	OS, PFS	Only Stage IV NSQ, TPS ≥50% subgroup treated with platinum+pemetrexed used in TPS ≥50% model

DB = double blind; 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.

<sup>a</sup> Patients with untreated central nervous system (CNS/brain) metastases were excluded from the KN189 study for the indirect comparisons as both the KN042 and KN024 had excluded patients with this disease characteristic.

<sup>b</sup> The "low" risk of bias was only based on the assessment of risk for the individual studies in isolation. For TPS ≥50% patients, the indirect comparisons using the KN189, KN024 and KN042 studies were associated with a high risk of bias.

<sup>c</sup> KN024 ITT population included both squamous and non-squamous patients.

<sup>d</sup> KN042 ITT population included Stage IIIb and Stage IV, squamous and non-squamous, TPS ≥1% patients.

<sup>e</sup> Sourced from Table 2.4.5, Appendix 25 accompanying the resubmission.

<sup>f</sup> Median duration of follow up was: 18.7 months for the ITT, 16.7 months for TPS <50%, 19.6 months for TPS ≥50%.

Source: Compiled during the evaluation based on Section 2 of, and Appendices 20 and 25 accompanying the resubmission.

6.8 The indirect comparisons were performed using the hazard ratio (HR) based on the Bucher method, after weighting population characteristics across the treatment arms using Inverse Probability of Treatment Weighting (IPTW). The same approach was used for the previous submission with an additional study (KN042) included in the resubmission.

### Comparative effectiveness

#### ITT, PD-L1 TPS <50% and ≥50% patient subgroups: pembrolizumab+platinum+pemetrexed vs platinum + pemetrexed: direct evidence

6.9 The results for the ITT and PD-L1 TPS <50% and ≥50% populations from the direct randomised KN189 trial are presented in Table 7. Kaplan-Meier curves for the ITT population (Figure 1) and PD-L1 TPS <50% population (Figure 2) in KN189 are presented below.

**Table 7: Overall survival and progression free survival results in KN189**

	Pembro Combo	Platinum+pemetrexed	Hazard ratio <sup>a</sup>
<b>Overall survival</b>			
Resubmission: Median duration of follow-up 18.7 months (Data cut-off September 2018)			
Previous submission: Median duration of follow-up 10.5 months (Data cut-off November 2017)			
All patients			
Median duration of follow-up 18.7 months			
No. of deaths at cutoff (%)	213/410 (52.0)	144/206 (69.9) <sup>b</sup>	<b>0.56 (0.45, 0.70)</b>
Median OS in months (95% CIs)	22.0 (19.5, 25.2)	11.3 (8.7, 15.1)	
Median duration of follow-up 10.5 months			
No. of deaths at cutoff (%)	127/410 (31.0)	108/206 (52.4)	<b>0.49 (0.38, 0.64)</b>
Median OS in months (95% CIs)	Not reached	11.3 (8.7, 15.1)	
PD-L1 TPS <■%			
Median duration of follow-up ■ months			
No. of deaths at cutoff (%)			
Median OS in months (95% CIs)			
Median duration of follow-up ■ months			
No. of deaths at cutoff (%)			
Median OS in months (95% CIs)			
PD-L1 TPS ≥50%			
Median duration of follow-up 19.6 months			
No. of deaths at cutoff (%)	58/132 (43.9)	42/70 (60.0)	<b>0.59 (0.39, 0.88)</b>
Median OS in months (95% CIs)	Not reached (20.4, NR)	10.1 (7.5, NR)	
Median duration of follow-up 10.5 months			
No. of deaths at cutoff (%)	34/132 (25.8)	36/70 (51.4)	<b>0.42 (0.26, 0.68)</b>
Median OS in months (95% CIs)	Not reached	10.0 (7.5, NR)	
<b>Progression free survival</b>			
All patients			
Median duration of follow-up 18.7 months			
No. of deaths/progressed at cutoff (%)	304/410 (74.1)	196/206 (92.2)	<b>0.48 (0.40, 0.58)</b>
Median PFS in months (95% CIs)	9.0 (8.1, 9.9)	4.9 (4.7, 5.5)	
Median duration of follow-up 10.5 months			
No. of deaths/progressed at cutoff (%)	244/410 (59.5)	166/206 (80.6)	<b>0.52 (0.43, 0.64)</b>
Median PFS in months (95% CIs)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)	
PD-L1 TPS <■%			
Median duration of follow-up ■ months			
No. of deaths/progressed at cutoff			
Median PFS in months (95% CIs)			
Median duration of follow-up ■ months			
No. of deaths/progressed at cutoff			
Median PFS in months (95% CIs)			

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	Pembro Combo	Platinum+pemetrexed	Hazard ratio <sup>a</sup>
PD-L1 TPS ≥50%			
Median duration of follow-up 19.6 months			
No. of deaths/progressed at cutoff	84/132 (63.6)	63/70 (90.0)	<b>0.36 (0.26, 0.51)</b>
Median PFS in months (95% CIs)	11.1 (9.1, 14.4)	4.8 (3.1, 6.2)	
Median duration of follow-up 10.5 months			
No. of deaths/progressed at cutoff	68/132 (51.5)	56/70 (80.0)	<b>0.36 (0.25, 0.52)</b>
Median PFS in months (95% CIs)	9.4 (9.0, 13.8)	4.7 (3.1, 6.0)	

Shaded data previously considered by PBAC

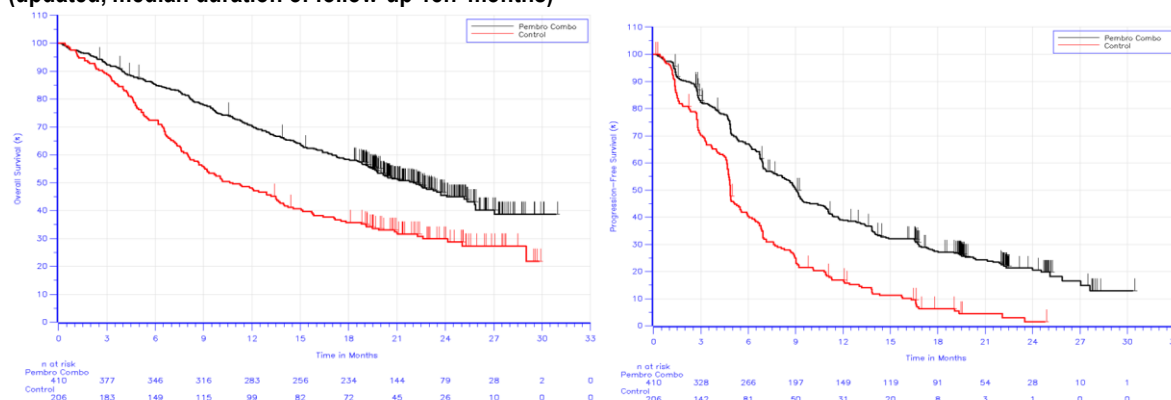
<sup>a</sup> Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).

<sup>b</sup> The number of events per number at risk (n/N) presented in Table 2.6.2, p72 of the resubmission (108/206 (52.4%)) appeared to be a “copy and paste” error from the earlier duration of follow-up (10.5 months) and has been replaced by updated data for the September 2018 data cutoff (18.7 months duration of follow-up: 144/206 (69.9%)) from Appendix 7 accompanying the resubmission, and corrected in the PSCR and Pre-PBAC responses.

Pembro Combo = pembrolizumab+platinum+pemetrexed; OS = overall survival; PFS = progression-free survival; **bold** = statistically significant

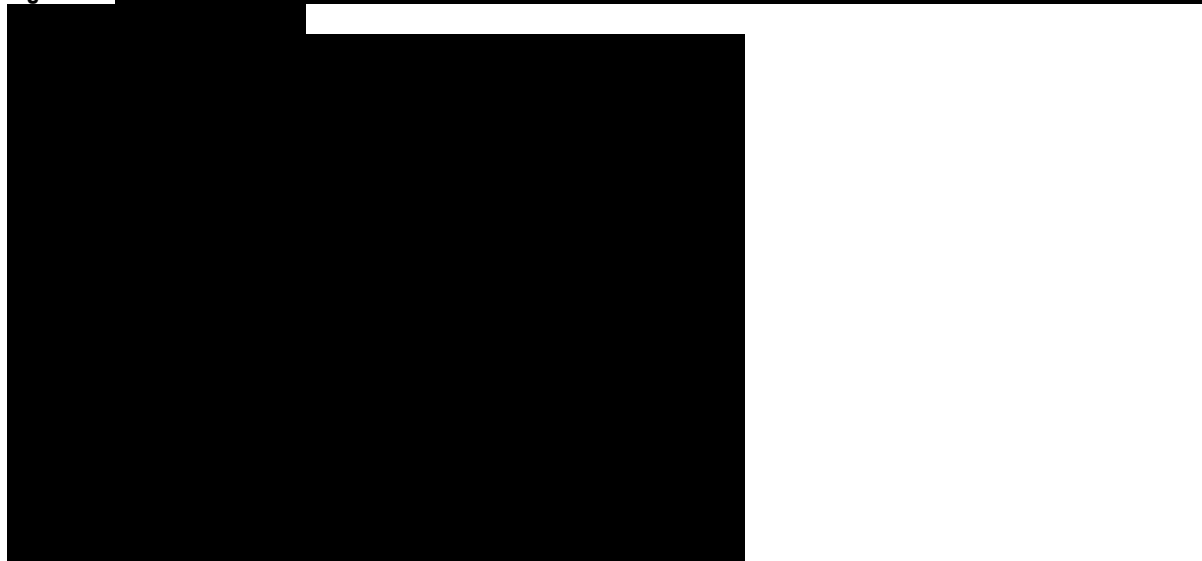
Source: Tables 2.6.2-3, pp72-74 of the resubmission and Table 6, p11 of Ratified 6.06 CiC pembrolizumab MINS 11-2018 for the data presented in the previous submission.

**Figure 1: Kaplan-Meier curve for overall survival (left) and progression-free survival (right) in KN189 ITT population (updated, median duration of follow-up 18.7 months)**



Source: Figures 2.5.2-3, pp57-8 of the resubmission.

Figure 2:



Source: Appendix 17 to the resubmission. The corresponding PFS curves for this subgroup were not presented in the resubmission.

- 6.10 A statistically significant improvement in OS and PFS was reported for the ITT, and PD-L1 TPS <50% and ≥50% populations treated with pembrolizumab+platinum+pemetrexed compared with platinum+pemetrexed followed by anti PD-(1)L therapy. This was consistent with the results presented in the previous submission.
- 6.11 The PD-L1 TPS <50% subgroup analysis in KN189 formed the key evidence to support the clinical claim regarding pembrolizumab+platinum+pemetrexed vs. platinum+pemetrexed followed by anti PD-(1)L therapy. Pembrolizumab+platinum+pemetrexed was associated with a longer median OS duration (■■■ months vs. ■■■ months; difference ■■■ months). The difference in median PFS also favoured pembrolizumab+platinum+pemetrexed.
- 6.12 No updated quality of life (QoL) data from KN189 were presented in the resubmission. 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.

**PD-L1 TPS ≥50% patient subgroup: pembrolizumab+platinum+pemetrexed versus pembrolizumab monotherapy: indirect evidence**

- 6.13 The results of the indirect comparison, in terms of OS and PFS, for pembrolizumab+platinum+pemetrexed versus pembrolizumab monotherapy are summarised in Table 8 and Table 9, respectively.

**Table 8: Indirect treatment comparison overall survival (KN189 vs. KN042+KN024: TPS ≥ 50%, weighted)**

Study ID	Pembro Combo <sup>a</sup>		Chemotherapy <sup>a</sup>		Pembro Mono <sup>a</sup>		Weighted <sup>e</sup> HR <sup>d, e</sup> [95 % CI]
	Patients with Event n/N <sup>b</sup> (%)	Median OS <sup>c</sup> Months [95 % CI]	Patients with Event n/N <sup>b</sup> (%)	Median OS <sup>c</sup> Months [95 % CI]	Patients with Event n/N <sup>b</sup> (%)	Median OS <sup>c</sup> Months [95 % CI]	
KN189 <sup>g</sup>	-	-	-	-	-	-	-
KN042+ KN024 <sup>h</sup>	-	-	-	-	-	-	-
[Redacted]							-

TPS = tumour proportion score; Pembro Combo = pembrolizumab+platinum+pemetrexed; Pembro Mono = pembrolizumab monotherapy; OS = overall survival; HR = hazard ratio; CI = confidence interval; NR = not reached; ITC = indirect treatment comparison.

<sup>a</sup>Pemetrexed and Carboplatin or Pemetrexed and Cisplatin for KN189 and KN024 and Pemetrexed and Carboplatin for KN042

<sup>b</sup>Number of patients: intention-to-treat, non-squamous subjects pre-assigned to carboplatin+pemetrexed or pemetrexed+cisplatin with TPS ≥ 50%, Patients in each arm in KN189 included in the indirect comparison were those who matched the population in the Pembro Mono studies, by excluding patients with untreated brain metastasis. This exclusion resulted in 121 patients in the Pembro Combo arm and 65 in the platinum+pemetrexed arm in KN189.

<sup>c</sup>From product-limit (Kaplan-Meier) method

<sup>d</sup>Based on Cox regression model with treatment as a covariate stratified by platinum chemotherapy (Cisplatin vs. Carboplatin) and smoking status (never vs. former/current) for KN189, and stratified by study (KN042 vs. KN024) for KN042+KN024. Individual study's stratification factors ECOG PS (0 vs. 1) and geographic region (East Asia vs. non-East Asia) are also covariates for KN042+KN024

<sup>e</sup>The inverse probability of treatment weighting (IPTW) method using a multinomial logistic regression was performed with covariates: smoking status (never vs. former/current), ECOG PS (0 vs. 1), age, gender and metastatic stage M1B (yes vs. no). The derived weights were used in the Cox model to adjust for population imbalance across studies and treatment arms

<sup>f</sup>Bucher methodology using separate study results (estimate and its standard error) with a common control arm to perform indirect comparison of effect of pembrolizumab combination (KN189) vs monotherapy (KN042+KN024)

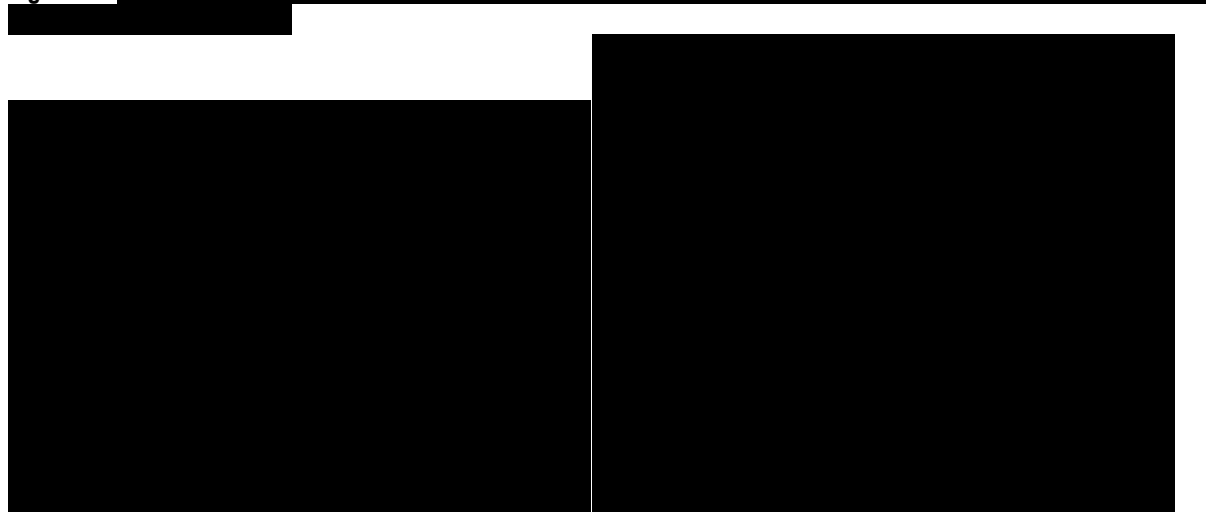
<sup>g</sup>Database Cutoff Date: 21SEP2018

<sup>h</sup>Database Cutoff Date: 04SEP2018 (KN042), 10JUL2017 (KN024)

Source: Tables 3 and 12, pages 27 and 40 of Appendix 20 accompanying the resubmission.



Figure 3:



Source: Figure 3, p26, Figure 6, p34 and Appendix 20 accompanying the resubmission

- 6.15 Based on the indirect comparison presented, the resubmission concluded that pembrolizumab+platinum+pemetrexed was associated with a statistically significant increase in PFS compared with pembrolizumab monotherapy (PFS HR = [REDACTED], 95% CI: [REDACTED]).
- 6.16 The resubmission noted that: a) the OS HR from the indirect comparison was not statistically significant, but numerically favoured pembrolizumab+platinum+pemetrexed, and b) the median OS in the pembrolizumab+platinum+pemetrexed arm of KN189 was not reached, whereas it was [REDACTED] months in the KN024/42 combined group. There are limitations associated with the HR estimates (see below). Notwithstanding these limitations, the only indirect estimate of efficacy that statistically significantly favoured pembrolizumab+platinum+pemetrexed was the PFS HR derived from the comparison between KN189 and KN024+KN042 (Table 9). There were no statistically significant differences in OS, between pembrolizumab+platinum+pemetrexed and pembrolizumab monotherapy, from the indirect comparisons (Table 8).
- 6.17 The evaluation considered, similar to the previous submission, the indirect comparison between pembrolizumab+platinum+pemetrexed and pembrolizumab monotherapy (KN189 vs. KN024+KN042) presented in the resubmission remained highly uncertain, as a result of both methodological and transitivity issues.
- The use of HRs was inappropriate in quantifying the magnitude of clinical benefit gained where there was departure from the proportional hazards (PH) assumption in the included studies. Figure 3 above indicated there was such a departure as the OS and PFS curves crossed for KN024+KN042.

- The inclusion of KN042 in the indirect comparison favoured pembrolizumab+platinum+pemetrexed. The relative benefit of pembrolizumab differed across the KN042 and KN024 studies.
- From the Kaplan Meier curves for OS and PFS (Figure 3), the absolute PFS and OS durations differed, between the common reference arms, across the KN189 and the pembrolizumab monotherapy studies. The median OS of the common reference arms (platinum+pemetrexed) was [REDACTED] months for the pembrolizumab monotherapy studies compared to [REDACTED] months for KN189 (Table 8).
- As in the previous submission, the resubmission used the IPTW approach to “balance” unequal distributions in specific baseline characteristics, within and across studies, for the indirect comparisons. Matched or weighted indirect comparisons may not mitigate the issue of confounding in indirect comparisons as weighting for numerous covariates (at the expense of precision) and for unknown confounders is not feasible.

**Pembrolizumab+platinum+pemetrexed versus ABCP: Naïve indirect evidence**

- 6.18 The resubmission presented a naïve indirect comparison between pembrolizumab+platinum+pemetrexed (KN189) and ABCP from the IMpower 150 trial. IMpower 150 compared ABCP to bevacizumab+carboplatin+paclitaxel (BCP) in previously untreated stage IV NSQ NSCLC. The resubmission noted that a common reference arm to enable an adjusted indirect comparison between pembrolizumab+platinum+pemetrexed and ABCP was lacking. This was because the comparator arm for ABCP in IMpower 150 was bevacizumab + a platinum doublet and the comparator arm for pembrolizumab+platinum+pemetrexed in KN189 was a platinum doublet only.
- 6.19 The resubmission concluded that there was a greater reduction (44%) in the “risk” of death associated with pembrolizumab+platinum+pemetrexed (KN189: HR = 0.56), compared to that associated with ABCP from the IMpower 150 trial (HR = 0.78; 22% reduction). The evaluation considered this claim was inadequately supported given the naïve nature of the analysis, different comparator arms and other potential differences in study design and patient populations not assessed in the resubmission.
- 6.20 The resubmission also stated that the above conclusions were supported by a published Bayesian network meta-analysis (NMA) which examined the comparative efficacy of pembrolizumab+platinum+pemetrexed specifically, relative to other regimens used in metastatic NSQ NSCLC trials, in patients without targetable mutations. Insufficient detail was provided in the submission regarding the conduct of the NMA to evaluate its validity. The PSCR provided substantial additional detail regarding the conduct of the NMA but the ESC noted the additional information was not evaluated.

## Comparative harms

6.21 Compared to the previous submission, the resubmission stated that:

- Updated data with 18.7 months follow up for KN189 have not changed safety conclusions; and
- There were no updates made since the previous submission to overall safety data, data on drug-related AEs and serious drug-related AEs.

6.22 The summary of key adverse events (AEs) in KN189 considered by the PBAC previously is re-produced in Table 10. Overall, the frequency of AEs was higher in patients treated with pembrolizumab+platinum+pemetrexed compared to patients treated with platinum doublet. The incidence of AEs of special interest was also higher in patients treated with pembrolizumab+platinum+pemetrexed compared to platinum doublet, with three patients dying due to pneumonitis in the pembrolizumab+platinum+pemetrexed group.

Table 10: Summary of statistically significant adverse events in KN189

Event	Pembro Combo, 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 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>	<b>0.04 (0.00, 0.07)</b>
Discontinue due to drug related 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>
Drug related 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>

Shaded data previously considered by PBAC

Pembro Combo = pembrolizumab+platinum+pemetrexed; AE = Adverse event; AEOSI = Adverse events of special interest; CI = confidence interval; n = number of participants reporting data; N = total participants in group; NC = not calculated; OR = odd ratio; RD = risk difference; RR = relative risk; **bold** = statistically significant

Source: Table 9, pembrolizumab (NSCLC) Public Summary Document, November 2018.

## Benefits/harms

6.23 A summary of the comparative benefits and harms for pembrolizumab+platinum+pemetrexed versus platinum+pemetrexed, in patients with tumours that are PD-L1 TPS <50%, is presented in Table 11.

Table 11: Summary of comparative benefits and harms for pembrolizumab+platinum+pemetrexed versus platinum doublet

Outcome	Pembro Combo	Platinum doublet	Absolute difference	HR (95% CI)		
<b>Benefits</b>						
<b>Time-to-event outcome OS: KN189 (PD-L1 TPS &lt;50%) – median duration of follow up 16.7 months</b>						
Deaths, n/N (%)	142/255 (55.7)	91/121 (75.2)		0.56 (0.43, 0.73) P=0.00001		
Median (mths)	19.8 (17.2, 22.8)	11.4 (8.6, 13.5)	8.4			
Survival at 6 months (%)	83.9 (78.7, 87.9)	76.0 (67.4, 82.7)	7.9			
<b>Time-to-event outcome PFS: KN189 (PD-L1 TPS &lt;50%) – median duration of follow up 16.7 months</b>						
Progressed, n/N (%)	202/255 (79.2)	112/121 (92.6)		0.58 (0.46, 0.74) P<0.00001		
Median (mths)	8.1 (6.8, 9.0)	4.9 (4.7, 6.5)	3.2			
PFS at 6 months (%)	61.9 (55.6, 67.6)	42.1 (33.1, 50.7)	19.8			
<b>Harms – median duration of follow-up: 10.5 months</b>						
Adverse event	Pembro Combo n/N (%)	Platinum doublet n/N (%)	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Pembro Combo	Platinum doublet	
Diarrhoea	125 (30.9)	43 (21.3)	<b>1.45 (1.08, 1.97)</b>	30.9	21.3	<b>0.10 (0.02, 0.17)</b>
Rash	82 (20.2)	23 (11.4)	<b>1.78 (1.17, 2.74)</b>	20.2	11.4	<b>0.09 (0.03, 0.15)</b>
Febrile neutropenia	24 (5.9)	4 (2.0)	<b>2.99 (1.05, 8.51)</b>	5.9	2.0	<b>0.04 (0.00, 0.07)</b>
Colitis	9 (2.2)	0 (0.0)	NC	2.2	0	<b>0.02 (0.00, 0.04)</b>
Hypothyroidism	27 (6.7)	5 (2.5)	<b>2.69 (1.05, 6.89)</b>	6.7	2.5	<b>0.04 (0.00, 0.07)</b>

Shaded data previously considered by PBAC

HR = hazard ratio; NC = not calculable; OS = overall survival, PFS = progression free survival; RD = risk difference; RR = risk ratio, **bold** = statistically significant

Source: Tables 2.6-2 and 2.6-3, pp72-74 of the resubmission and Table 10 in the previous evaluation (6.06.COM.15, November 2018).

6.24 On the basis of direct evidence presented in the resubmission, for every 100 patients with tumours that have PD-L1 <50% and are treated with pembrolizumab+platinum+pemetrexed in comparison with platinum+pemetrexed:

- Approximately 20 additional patients would be progression-free 6 months after the start of treatment; and
- Approximately 8 additional patients would be alive 6 months after the start of treatment.

6.25 These data were consistent with those presented in the previous submission.

6.26 The relative safety data for pembrolizumab+platinum+pemetrexed with platinum+pemetrexed were unchanged from the previous submission. On the basis of direct evidence presented by the submission, for every 100 patients treated with pembrolizumab+platinum+pemetrexed in comparison to platinum doublet and over a median duration of follow-up of 10.5 months (regardless of PD-L1 expression):

- Approximately 10 additional patients would have diarrhoea.
- Approximately 9 additional patients would have rash.
- Approximately 4 additional patients would have febrile neutropenia.
- Approximately 2 additional patients would have colitis.

- Approximately 4 additional patients would have hypothyroidism.
- 6.27 Given the uncertainty associated with the indirect comparisons between pembrolizumab+platinum+pemetrexed and pembrolizumab monotherapy, the lack of a significant difference in OS benefit between the two treatments, and the naïve nature of the comparisons for safety data, a benefits/harms table has not been presented for the population with tumours that are PD-L1 TPS  $\geq$ 50%.

### **Clinical claim**

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

- 6.28 The resubmission claimed that pembrolizumab+platinum+pemetrexed was superior in terms of effectiveness, and inferior in terms of safety, to platinum+pemetrexed (platinum doublet) followed by anti PD-(L)1 therapy, in patients with PD-L1 TPS <50%.
- 6.29 The PBAC previously considered the claim of superior comparative effectiveness of pembrolizumab+platinum+pemetrexed versus platinum+pemetrexed was not adequately supported by the data presented in the previous submission, given the concern over the immaturity of KN189 OS data, and the uncertain extent of subsequent anti PD(L)-1 inhibitor use post-progression, in the platinum+pemetrexed arm in KN189 for the PD-L1 TPS <50% subgroup.
- Compared with the previous submission, the resubmission provided an additional 6 months of data from KN189 to support the claim of superior effectiveness of pembrolizumab+platinum+pemetrexed versus platinum+pemetrexed.
  - The resubmission provided new information which indicated that, for the TPS <50% population, 88% of patients who received a 2<sup>nd</sup> line treatment received an anti-PD-(L)1 agent. This extent of subsequent use of PD(L)-1 inhibitors post-progression with chemotherapy appeared to be a reasonable reflection of the second line PD(L)-1 inhibitor use in the Australian clinical practice.
- 6.30 The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data.
- 6.31 The PBAC considered that the claim of inferior comparative safety was reasonable.

**PD-L1 TPS ≥50% patient subgroup**

- 6.32 The resubmission described pembrolizumab+platinum+pemetrexed as superior in terms of “survival” and “inferior but manageable safety” compared with pembrolizumab monotherapy in patients with PD-L1 TPS ≥50%.
- 6.33 Similar to the previous submission, the resubmission’s superiority claim for pembrolizumab+platinum+pemetrexed versus pembrolizumab monotherapy was based on an indirect comparison using KN189, KN024 and KN042 trials, which remained highly uncertain, as a result of both methodological and transitivity issues as described above. Furthermore, the indirect comparison in the resubmission did not show that there was a statistically significant benefit in OS associated with pembrolizumab+platinum+pemetrexed relative to pembrolizumab monotherapy followed by a platinum doublet.
- 6.34 The PBAC previously considered that the transitivity of the three studies had not been adequately addressed. The PBAC also 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. Consequently, the 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 (paragraphs 7.8 and 7.9, pembrolizumab (NSCLC) PSD, November 2018). The new information provided in the resubmission did not address the PBAC’s previous concerns regarding the comparative effectiveness of pembrolizumab+platinum+pemetrexed with pembrolizumab monotherapy, in the PD-L1 TPS ≥50% population.

***Economic analysis***

- 6.35 The resubmission presented two economic evaluations (Table 12):
- PD-L1 TPS <50%: pembrolizumab+platinum+pemetrexed vs. platinum + pemetrexed. A modelled economic evaluation based on the results of a subgroup in the direct-randomised trial (KN189);
  - PD-L1 TPS ≥50%: pembrolizumab+platinum+pemetrexed vs. pembrolizumab monotherapy. A modelled economic evaluation based on an indirect comparison of subgroups from randomised trials (KN189 versus KN024 and KN042).
- 6.36 The types of economic evaluations presented were cost-utility analyses. The type of economic evaluation for the PD-L1 TPS <50% population was appropriate and consistent with the evidence base presented above.

6.37 Regarding the economic analysis for the PD-L1 TPS  $\geq 50\%$  group, the PBAC previously 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 OS between pembrolizumab monotherapy and pembrolizumab+platinum+pemetrexed. The ESC noted the PSCR did not revise the clinical claim of superiority, but offered a discount on the price of pembrolizumab when used as part of combination therapy “to deliver an incremental cost effectiveness ratio (ICER) of \$0 relative to monotherapy treatment” (\$█████ per 100 mg via in the PSCR compared to \$█████ in the resubmission). The PBAC reiterated that a cost utility analysis was not appropriate for this population but noted that with the price reduction offered, the cost per patient per treatment course for pembrolizumab+platinum+pemetrexed and pembrolizumab monotherapy was similar.

**Table 12: Key components of the economic evaluation**

Component	Description
Type of analysis	Cost utility and cost effectiveness analysis
Outcomes	QALY, LYG
Time horizon	7.5 years
Methods used to generate results	Partitioned survival analysis
Health states	Pre-progression, progression and death
Time interval in which health state membership is determined, and cost and outcomes are accrued (cycle)	1 week. This appeared reasonable.
Health state membership	PD-L1 TPS <50%: based on KM curve from subgroup of KN189, separately extrapolated. There was convergence of PFS and OS curves towards the end of the time horizon of the model.  PD-L1 TPS $\geq 50\%$ : pembro combo arm based on KM curve from subgroup of KN189 and extrapolated. HR from ITC in Section 2 used to determine Pembro Mono arm. Forced convergence of PFS and OS curves
Utilities	Application determined by health state membership. Utilities based on KN189 for pembrolizumab+platinum+pemetrexed and platinum+pemetrexed arms. Utilities for pembrolizumab monotherapy from KN024, adjusted for differences in platinum+pemetrexed arm.
Discount rate	5% per annum for cost and outcomes
Software package	Microsoft Excel 2010

Pembro Combo = pembrolizumab+platinum+pemetrexed; Pembro Mono = pembrolizumab monotherapy; QALY = quality-adjusted life year; LYG = life year gained; PD-L1 = programmed death ligand 1; TPS = tumour proportion score; PFS = progression free survival; OS = overall survival; HR = hazard ratio; ITC = indirect treatment comparison.

Source: Table 3.1-2, Section 3 of the resubmission

- 6.38 Consistent with feedback from the PBAC on the November 2018 PBAC submission, the resubmission applied utilities by the patient’s progression-status (i.e., progression-free; progressive disease) instead of utilities by time-to death. This change was appropriate. However, the ESC noted that the utility values in the original submission could not be verified, and that insufficient detail was provided in the resubmission to assess the appropriateness of the revised utilities. The ESC also noted that utility values were higher in the resubmission than those in the original submission, for each health state and for each treatment arm. The ESC noted a large amount of information on utilities was provided with the PSCR but the information was not considered informative as it was not able to be evaluated due to the timeframe in which it was provided.
- 6.39 The resubmission stated that the utility values for progression-free and progressive disease health states for the pembrolizumab+platinum+pemetrexed and platinum+pemetrexed arms were obtained from the EQ-5D results from KN189, using Australian-based valuations. For the pembrolizumab monotherapy arm, EQ-5D utility data were from the KN024 trial with an adjustment to account for different patient characteristics between KN024 and KN189. The utility values were derived by multiplying the ratio of the pembrolizumab monotherapy treatment arm and the chemotherapy treatment arm utilities in KN024 by the chemotherapy treatment arm utilities in KN189 (e.g., for the progression free state,  $0.779/0.742 = 1.05$ , utilities =  $1.05 \times 0.766 = 0.804$ ). The utility weights for pembrolizumab monotherapy and the utilities used in the base case of the economic models are summarised in the tables below.

**Table 13: Utility weights for Pembrolizumab Monotherapy**

Health State	Pembro Mono in KN024	Chemotherapy in KN024	KN024 Ratio (pembro:chemo)	Modelled Values for Pembro mono
Progression-free	0.779	0.742	1.05	0.804
Progressive	0.665	0.679	0.98	0.677

Source: Table 3.5-2 Section 3 of the submission

**Table 14: Health state utilities used in the base case of the economic models**

Health State	Pembrolizumab+platinum+pemetrexed	Platinum+pemetrexed	Pembro Mono
Progression-free	0.776	0.766	0.804
Progressive	0.714	0.691	0.677

Source: Table 3.5-1 and 3.5-2 Section 3 of the submission.

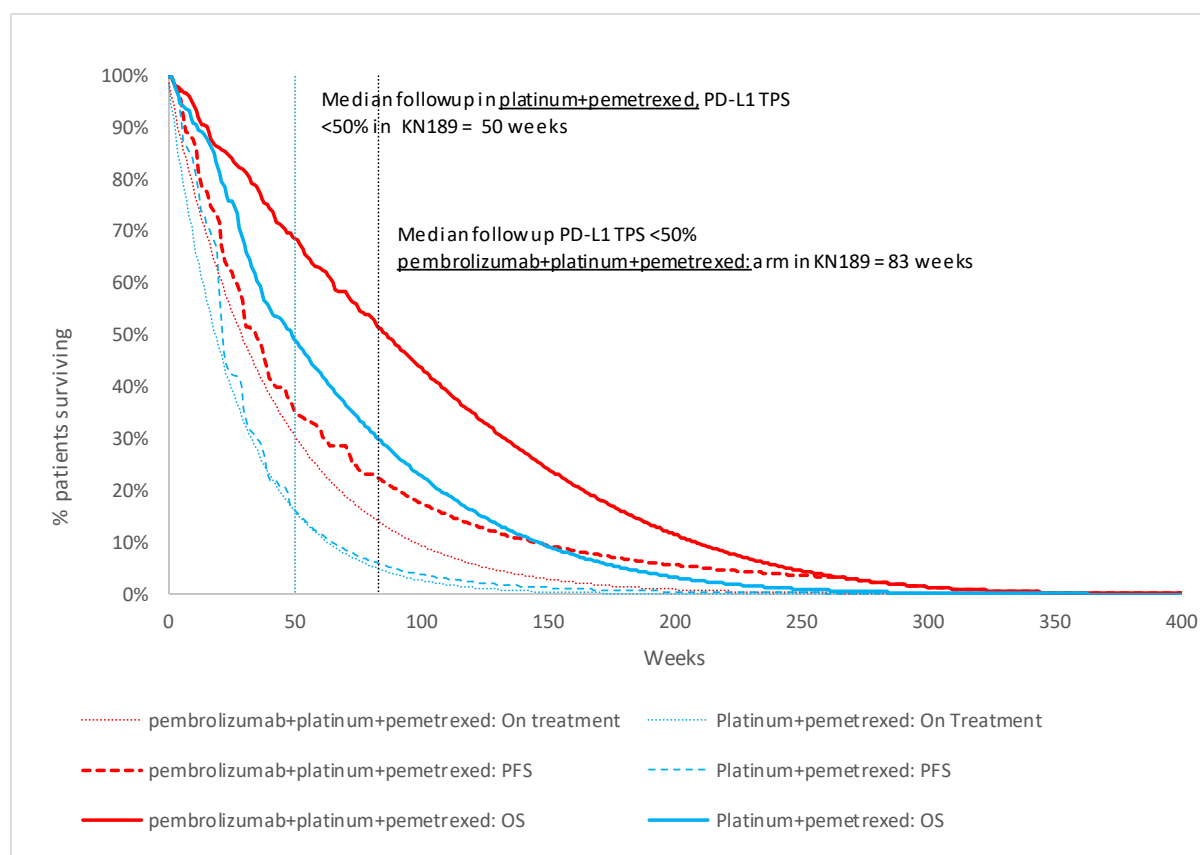
- 6.40 The ESC considered it was unclear why the utility for pembrolizumab+platinum+pemetrexed would be higher than the utility for those in the platinum+pemetrexed arm for both the progression-free and progressive disease states, especially given the higher rate of AEs seen with pembrolizumab+platinum+pemetrexed. The PSCR argued that the higher utility in the pembrolizumab+platinum+pemetrexed arm reflected the EQ-5D results collected in KN189 trial, which were consistent with the EORTC QLQ-C30 GHS/QoL results also collected in KN189. The Pre-PBAC response argued that as not all EQ-5D dimensions are influenced by the presence of AEs, the fact that pembrolizumab+platinum+pemetrexed is associated with more AEs does not translate directly to lower utilities for that group. In addition, the pre-PBAC response argued that patients receiving pembrolizumab+platinum+pemetrexed might have less symptom burden in both the progression-free and progressive-disease state compared to patients receiving chemotherapy alone, which may lead to their higher perceived quality of life and utility values.
- 6.41 The resubmission used the proposed effective price of pembrolizumab (when in combination with platinum and pemetrexed) in the base case of the economic evaluation. The resubmission assumed an average cost of nivolumab per treated patient in the second line setting based on previous deed negotiations.
- 6.42 The resubmission made a number of key changes to the derivation of healthcare resource use and costs in both economic models that were consistent with previous PBAC and ESC considerations:
- The proportion of patients receiving any post-discontinuation treatment was sourced directly from the specific population (PD-L1 TPS <50% vs PD-L1 TPS ≥50%) in KN189, rather than a pooled estimate across the entire trial population regardless of PD-L1 status. This change was appropriate and consistent with PBAC feedback.
  - The duration of treatment with nivolumab in the platinum+pemetrexed arm following progression remained at 24 weeks, consistent with PBAC advice.
  - The vial price of pembrolizumab was reduced from the previous submission (refer to paragraph 2.2). The resubmission did not justify a higher price in the PD-L1 TPS <50% population than that for the PD-L1 TPS ≥50% population.
  - Minor updates to the cost of pre-medications, and concomitant medications were also incorporated. This included price reductions associated with pemetrexed, although did not incorporate the statutory price reduction that occurred on 1 April 2019.

- 6.43 The PSCR provided revised economic models, incorporating several changes in response to the evaluation as well as additional changes such as the proportion of patients treated in a public/private hospital setting (the proportion of patients treated in the public hospital setting increased from 32.7% to 34.4%). The ESC noted the revised economic models were not evaluated.

**PD-L1 TPS <50% economic model**

- 6.44 For the PD-L1 TPS <50% population, the main differences in the economic models between the November 2018 submission and the current resubmission in relation to the estimation and extrapolation of treatment effect were:
- PFS, OS and time on treatment (ToT) KM estimates were based on updated efficacy data from KN189 with an additional 6 months follow up. The resubmission appropriately refitted the parametric functions used for extrapolation.
  - Consistent with previous ESC and PBAC advices, the resubmission used individually fitted parametric functions to extrapolate the KM data from median follow up.
  - Consistent with previous ESC advice, the resubmission used the Gompertz parametric function to extrapolate OS. This remains the most conservative extrapolation; and
  - The resubmission used the log-normal parametric function to extrapolate the PFS curve and exponential function to extrapolate the ToT curve. Given the maturity of the updated data for PFS and ToT, the choice of extrapolation functions did not substantially alter the results of the model.
- 6.45 The modelled PFS, OS and ToT curves for the pembrolizumab+platinum+pemetrexed and platinum+pemetrexed arms are provided in the figures below.

Figure 4: PD-L1 TPS <50%: Modelled PFS, OS and ToT for the pembrolizumab+platinum+pemetrexed and platinum+pemetrexed arms



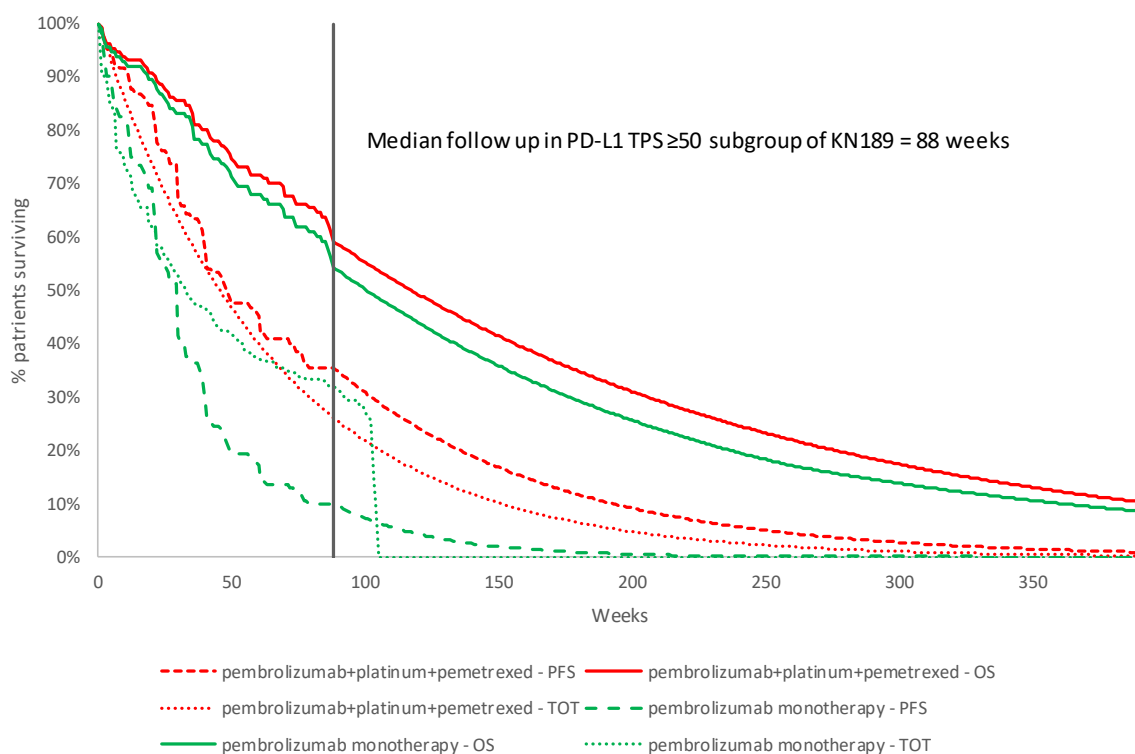
Source: compiled during the evaluation based on information presented in 'KN189 NSQ NSCLC Under 50 CE PD-L1 FINAL 05MAR19.xlsx'

### PD-L1 TPS ≥50% economic model

6.46 The resubmission made a number of changes to the allocation of health state membership over time:

- PFS, OS and ToT KM estimates for the pembrolizumab+platinum+pemetrexed arm were based on the updated efficacy data from KN189 with an additional 6 months follow up. The resubmission appropriately refitted the parametric functions used for extrapolation;
- Updated HR of PFS and OS for pembrolizumab+platinum+pemetrexed versus pembrolizumab monotherapy, based on the results of the updated ITC;
- The extrapolated PFS curves in the pembrolizumab+platinum+pemetrexed and pembrolizumab monotherapy arms and OS curves in these two comparative arms were forced to converge, beginning at week 130 (approximately 2.5 years) and converging at 7.5 years (the end of the time horizon), for both OS and PFS.

**Figure 5: PD-L1 TPS  $\geq 50\%$ : Modelled PFS, OS and ToT curves for the pembrolizumab+platinum+pemetrexed and pembrolizumab monotherapy arms**



Note: the maximum duration of pembrolizumab in combination with platinum and pemetrexed was capped at 2 years, consistent with the proposed listing. Source: Compiled during the evaluation based on information presented in 'KN189 NSQ NSCLC Over 50 CE PD-L1 FINAL 05MAR19.xlsx'

- 6.47 In the pembrolizumab monotherapy arm, follow-up on the ToT outcome in KN024 was complete and, therefore, the model employed the KM curve for this outcome directly rather than using parametric survival functions. The ToT KM curve for pembrolizumab monotherapy lay substantially above the modelled PFS curve (see Figure 5), which suggested that the estimated PFS curve may not be appropriate.
- 6.48 The results of the economic evaluations are provided in Table 15 (PD-L1 TPS  $< 50\%$ ) and Table 16 (PD-L1 TPS  $\geq 50\%$ ) below.

**Table 15: Results of the economic evaluation for the PD-L1 TPS <50% population; current resubmission and November 2018 submission**

Component	Pembro Combo	Platinum+pemetrexed	Increment
<b>Current resubmission</b>			
Life years gained (LYG)	1.85	1.24	0.61
QALY gained	1.39	0.90	0.49
Cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Incremental cost per LYG (PD-L1 TPS <50%)			\$ [REDACTED]
Incremental cost per QALY gained (PD-L1 TPS <50%)			\$ [REDACTED]
<b>November 2018 submission</b>			
Life years gained (LYG)	2.23	1.41	0.82
QALY gained	1.62	0.99	0.63
Cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Incremental cost per LYG (PD-L1 TPS <50%)			\$ [REDACTED]
Incremental cost per QALY gained (PD-L1 TPS <50%)			\$ [REDACTED]

Shaded data previously considered by PBAC

LYG = life years gained; QALY = quality-adjusted life year; PD-L1 = Programmed death-ligand 1; Pembro Combo = pembrolizumab + platinum+ pemetrexed; TPS = tumour proportion score

Note: calculations based on the figures above may differ to results in this table due to rounding.

Source: Table 3.8-6 and Table 3.8-7 Section 3 of the resubmission and Table 3.8.1 in 6.06 pembrolizumab COM 11-2018

The redacted table shows ICERs in the range \$15,000/QALY - \$45,000/QALY to \$45,000/QALY - \$75,000/QALY.

**Table 16: Results of the economic evaluation for the PD-L1 TPS ≥50% population; current resubmission and November 2018 submission**

Component	Pembro Combo	Pembro Mono	Increment
<b>Current resubmission</b>			
Life years gained (LYG)	2.71	2.55	0.16
QALY gained	2.03	1.81	0.21
Cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Incremental cost per LYG (PD-L1 TPS ≥50%)			\$ [REDACTED]
Incremental cost per QALY gained (PD-L1 TPS ≥50%)			\$ [REDACTED]
<b>November 2018 submission</b>			
Life years gained (LYG)	2.81	2.31	0.50
QALY gained	2.08	1.72	0.36
Cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Incremental cost per LYG (PD-L1 TPS ≥50%)			\$ [REDACTED]
Incremental cost per QALY gained (PD-L1 TPS ≥50%)			\$ [REDACTED]

Shaded data previously considered by PBAC

LYG = life years gained; QALY = quality-adjusted life year; PD-L1 = Programmed death-ligand 1; Pembro Combo = pembrolizumab + platinum+ pemetrexed; TPS = tumour proportion score

Note: calculations based on the figures above may differ to results in this table due to rounding.

Source: Table 3.8-8 and Table 3.8-9 Section 3 of the resubmission and Table 3.8.1 in 6.06 pembrolizumab COM 11-2018

The redacted table shows ICERs in the range \$15,000/QALY - \$45,000/QALY to \$45,000/QALY - \$75,000/QALY.

6.49 The results of key sensitivity analyses are provided in Table 17 below.

**Table 17: Results of selected univariate sensitivity analyses**

#	Variable (base case)	Change	ICER (\$/QALY)	
			PD-L1 TPS <50%:	PD-L1 TPS ≥50%:
1	Base case		\$ [REDACTED]	\$ [REDACTED]
2	Discount rate (5%)	0%	\$ [REDACTED]	\$ [REDACTED]
3		10%	\$ [REDACTED]	\$ [REDACTED]
4	Time horizon (7.5 years)	10 years	\$ [REDACTED]	\$ [REDACTED]
5		5 years	\$ [REDACTED]	\$ [REDACTED]
6	AE costs (Pembro combo =\$1,473; Pembro Mono = \$1,089; platinum+pemetrexed = \$46)	Halved: Pembro combo =\$737 Pembro Mono = \$544 platinum+pemetrexed = \$23	\$ [REDACTED]	\$ [REDACTED]
7		Doubled: Pembro combo =\$2,946 Pembro Mono = \$2,177 platinum+pemetrexed = \$92	\$ [REDACTED]	\$ [REDACTED]
8	Disease management costs <sup>^</sup>	Halved	\$ [REDACTED]	\$ [REDACTED]
9		Doubled	\$ [REDACTED]	\$ [REDACTED]
10		Disease management costs for the PFS health states in Pembro Combo arm set equal to the platinum+pemetrexed costs*	\$ [REDACTED]	\$ [REDACTED]
11	Terminal care costs	Halved	\$ [REDACTED]	\$ [REDACTED]
12		Doubled	\$ [REDACTED]	\$ [REDACTED]
13	Second line nivolumab use in platinum+pemetrexed arm	Increased by 10%	\$ [REDACTED]	\$ [REDACTED]
14		Decreased by 10%	\$ [REDACTED]	\$ [REDACTED]
15	Utilities	Applying utilities in the platinum+pemetrexed arm to the pembrolizumab+platinum+pemetrexed arm	\$ [REDACTED]	\$ [REDACTED]

Pembro Combo = pembrolizumab+platinum+pemetrexed; PD-L1 = Programmed death-ligand 1; PFS = progression-free survival; QALY = quality-adjusted life-year; TPS = tumour proportion score.

\*conducted during the evaluation. The resubmission did not make any adjustments to the derivation or application of disease management costs. As noted in the previous commentary, the higher weekly cost associated with the management of patients in the progression-free health state in the platinum+pemetrexed arm compared to the pembrolizumab+platinum+pemetrexed arm lacks face validity, and is not justified by either the original submission or resubmission.

<sup>^</sup>Disease management costs:

- Weekly management (year 1 and 2), progression free state: Pembro Combo and Pembro Mono=\$83.28; Platinum+pemetrexed=\$104.10
- Weekly management (year 3 +), progression free state: Pembro Combo and Pembro Mono= \$41.64; Platinum+pemetrexed =\$52.05
- Weekly management (all years), progressed disease: Pembro Combo and Pembro Mono=\$85.50; Platinum+pemetrexed= \$85.50
- Terminal care (death): \$6,278.44

Source: Table 3.9-1, Section 3 of the resubmission

6.50 For the PD-L1 TPS <50% population, the appropriateness of the utility values remains uncertain. The ESC noted that setting the utilities in the pembrolizumab+platinum+pemetrexed arm equal to those in the platinum+pemetrexed arm increased the ICER from \$45,000/QALY - \$75,000/QALY in the base case to \$45,000/QALY - \$75,000/QALY.

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

6.51 For the PD-L1 TPS <50% population, the cost per patient per course is:

- \$ [REDACTED] based on a mean duration of [REDACTED] doses (at 200 mg/dose) for pembrolizumab (\$ [REDACTED]) and an average of [REDACTED] doses of pemetrexed and 3.57 doses of platinum (\$2,723).
- This compared to an average price of \$2,451 for platinum+pemetrexed in the comparator arm. This estimate was based on an average of 9.53 doses of pemetrexed and 3.71 doses of platinum.

6.52 For the PD-L1 TPS ≥50% population, the cost per patient per course is:

- \$ [REDACTED] based on a mean duration of [REDACTED] doses (at 200 mg/dose) for pembrolizumab (\$ [REDACTED], using the price offered in the PSCR ) and an average of [REDACTED] doses of pemetrexed and 3.71 doses of platinum (\$3,943).
- This compared to an average price of \$ [REDACTED] per course for pembrolizumab monotherapy, assuming an average of [REDACTED] doses (at 200 mg/dose).

6.53 All calculations above assumed a public/private hospital split of 32.7% public hospital and 67.3% private hospital use and are based on the dispensed price in the relevant population.

6.54 There were some small differences between the average cost per course applied in Section 3 and Section 4:

- Data sources for the number of mean doses in the economic and financial models were consistent. However, the economic estimates multiplied the proportion of patients on treatment (according to the observed and extrapolated ToT curve) by the proportion of actual doses of planned doses as observed in KN189 and KN024.
- Prices applied in Section 3 differed from those applied in Section 4. Section 3 applied different prices per 100 mg vial of pembrolizumab in each of the populations (\$ [REDACTED] DPMA weighted between public and private hospital use in the PD-L1 TPS <50% population; and \$ [REDACTED] DPMA weighted between public and private hospital use in the PD-L1 TPS ≥50% population), whereas the Section 4 estimates used a single price for both populations (the nominated effective price for the listings). The effective price was weighted by the proportion of vials expected to be dispensed for each of these populations.

6.55 Using the revised weighted effective AEMP provided in the PSCR (\$ [REDACTED] per 100 mg vial) and applying a public/private hospital split of 32.7% / 67.3% use, the pembrolizumab cost per patient per course weighted across the PD-L1 TPS <50% population and the PD-L1 TPS ≥ 50% population is \$ [REDACTED] based on dispensed prices and \$ [REDACTED] including platinum chemotherapy and pemetrexed.

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

- 6.56 This resubmission was not considered by DUSC. The resubmission presented an epidemiological approach to estimating the financial impact of listing pembrolizumab+platinum+pemetrexed on the PBS for patients with NSQ, EGFR/ALK/ROS negative NSCLC.
- 6.57 The resubmission adopted the majority of the calculations for the revised patient numbers for pembrolizumab+platinum+pemetrexed from the PBAC Minutes (Table 15 and Table 16, Item 6.06 Pembrolizumab, November 2018 PBAC Meeting Minutes), with the exception of:
- The predicted uptake rate of PD-(L)1 inhibitors was revised from 81% to 85%, consistent with Department of Health background paper titled PD-(L)1 inhibitors for Non-Small Cell Lung Cancer.<sup>b</sup> The resubmission stated that this treatment rate has been accepted by the PBAC for the anti-PD-(L)1 treatment of NSCLC. The DUSC has previously considered 85% was reasonable.
  - The resubmission revised the expected market share of pembrolizumab+platinum+pemetrexed in the PD-L1 TPS  $\geq 50\%$  population from 80% to 30%, based on the FlatIron real-world database<sup>c</sup>. The FlatIron database may not be applicable to the Australian population, given the vast differences in health care systems between Australia and the United States that may influence treatment choice. The ESC considered that only a small proportion of patients in the PD-L1 TPS  $\geq 50\%$  population with a high disease burden would be treated with pembrolizumab+platinum+pemetrexed rather than pembrolizumab monotherapy.
- 6.58 The resubmission assumed that approximately 95% of all patients initiating treatment with platinum+pemetrexed would have received second line therapy with nivolumab (as a proxy for nivolumab and atezolizumab). The PBAC considered it was not appropriate to apply the 95% to the platinum+pemetrexed patients and not consistent with how the 5% uplift in patient numbers was applied in the pembrolizumab monotherapy deed negotiations.
- 6.59 The resubmission attempted to quantify the reduction in use of MBS Items, including those relating to administration costs, oncologist consultations and imaging, although did not calculate the total cost associated with these. The resubmission made a number of errors in the estimates of MBS Item usage. The PSCR provided an updated budget impact model incorporating corrections.

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<sup>b</sup> Outcome paper from the 8 February PBAC Special Meeting:

<http://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/stakeholder-meetings>

<sup>c</sup> 'FlatIron\_1L NSCLC Pembro Counts\_(Dec18).pdf' (unpublished), as supplied by the resubmission

6.60 The table below presents the estimated use and financial implications over six years from the resubmission.

**Table 18: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated <sup>a</sup>	█	█	█	█	█	█
Number of scripts dispensed <sup>b</sup>	█	█	█	█	█	█
<b>Estimated financial implications of pembrolizumab+platinum+pemetrexed</b>						
Pembrolizumab	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Pemetrexed <sup>c</sup>	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Carboplatin (72%)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cisplatin (28%)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total <sup>c</sup>	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cost to PBS/RPBS less copayments <sup>c</sup>	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Estimated reduction in use of other medicines (net of patient co-payments)</b>						
Cost to PBS/RPBS: Platinum+pemetrexed	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
PBS/RPBS: pembrolizumab monotherapy	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
PBS/RPBS: Second line nivolumab*	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total cost to PBS/RPBS net of copayments <sup>c</sup>	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Net financial implications</b>						
Net cost to PBS/RPBS <sup>c</sup>	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

<sup>a</sup> Includes 100 grandfathered patients in year 1.

<sup>b</sup> Assuming 10.75 administrations of pembrolizumab in year 1 and 5.61 administrations in year 2, based on the Time on Treatment curve from KN189.

<sup>c</sup> Revised to incorporate statutory price reduction of pemetrexed that occurred on 1 April 2019 that reduced the effective price of pemetrexed from \$9.24 per 100 mg vial to \$7.67 per 100 mg vial.

Source: compiled during the evaluation based on information presented in Section 4.

\* Using a confidential effective price

6.61 The updated budget impact model provided with the PSCR also incorporated the revised drug price for the TPS ≥50% population, and some other minor adjustments. The ESC noted the updated budget impact model was not evaluated.

6.62 The ESC noted the estimates provided in the resubmission were based on the previous consideration of pembrolizumab in this setting and did not take account of the approach agreed in the context of the post-PBAC negotiations for pembrolizumab monotherapy NSCLC listing (which took place in parallel with the previous PBAC submission for combination therapy).

6.63 The ESC noted revised estimates provided by the Department of Health, based on a similar approach as that used during the pembrolizumab monotherapy negotiations (Table 19 and Table 20). The ESC noted that these estimates were based on PD-(L)1

costs only and resulted in a net incremental cost of approximately \$20 - \$30 million per year. The estimated incremental PD-(L)1 cost applying the patient estimates in the resubmission are presented in Table 21. The PBAC noted there was a substantial difference in the number of new patients not offset by post-progression PD-(L) inhibitor use with the sponsor estimating less than 10,000 ■■■ per year and DoH estimating less than 10,000 per year.

- 6.64 The Pre-PBAC response stated that the sponsor is prepared to work with the Department of Health to determine the appropriate financial estimates. However, it highlighted that the calculations in Table 20 did not account for the number of patients diagnosed at Stage III that progressed to Stage IV. The Pre-PBAC response also requested grandfathering of an additional 400 (total 500) patients enrolled in the product familiarisation program.
- 6.65 The PBAC noted the comments in the pre-PBAC response regarding the progression of patients from Stage III to Stage IV. However, the PBAC considered the patient numbers in Table 20 correctly account for patients diagnosed at stage III who progress to Stage IV and are consistent with the approach accepted by the sponsor for the pembrolizumab monotherapy listing. The PBAC considered the estimates presented in Table 15 and Table 16, Item 6.06 Pembrolizumab of the November 2018 PBAC Meeting Minutes inadvertently double counted patients diagnosed at Stage III, noting these patients were already included in the currently agreed patient numbers (for pembrolizumab, nivolumab and atezolizumab in NSCLC).
- 6.66 The PBAC noted the sponsor had revised the number of patients who would require grandfathering onto PBS therapy from less than 10,000 in its resubmission (March 2019) to less than 10,000 in its pre-PBAC response (June 2019). The PBAC did not consider it appropriate for Government to meet the entire cost of the sponsor's early access program. The PBAC considered that any increase in the year 1 cap to allow for the cost of treating patients who commenced treatment prior to PBS listing should share the cost of treating grandfathered patients with the sponsor and should also take into consideration that some of these less than 10,000 patients are already accounted for in the patient number estimates. The PBAC considered it was reasonable to assume less than 10,000 patients are already included in the financial estimates (calculated as 1/12 of annual patient numbers). The PBAC further considered that it would be appropriate to assume the remaining less than 10,000 patients had already received 50% of their treatment course and that all would have received second line treatment with a PD-(L)1 inhibitor and should be offset.

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**Table 19: Assumptions and costs applied**

	Variable	Value	Source
A.	Proportion of Stage IV patients of all Stage IIIB/IV patients	78.6%	Mitchell et al. Lung cancer in Victoria: are we making progress? MJA 199 (10):18 November 2013.
B.	Proportion of NSCLC patients with non-squamous histology	77.6%	Systemic therapy treatment patterns in patients with advanced non-small cell lung cancer (NSCLC): PivOTAL study. European Journal of Cancer Care, February 2017.
C.	Proportion of non-squamous NSCLC patients who are EGFR, ROS or ALK negative	= 12.5% + 4% + 1.6% = 18.1%	EGFR and ROS previously agreed (July 2018 PBAC, item 7.17) 1.6% of NSCLC patients are estimated to be ROS positive [Crizotinib PSD, July 2018]
D.	2L nivolumab market potentially replaced by 1L pembrolizumab (either in combination with platinum-based chemotherapy and pemetrexed or as monotherapy)	49.95%	Calculated: A. x B. x (100-C.)
E.	2L NSQ and SQ nivolumab market potentially replaced by pembrolizumab monotherapy	19.53%	July 2018 PBAC, item 7.17
F.	2L NSQ nivolumab market potentially replaced by pembrolizumab monotherapy	15.15%	Calculated: E.x B.
G.	1st line pembrolizumab monotherapy replaced by 1st line pembrolizumab combination therapy	30%	Section 4 workbook
H.	New 1 <sup>st</sup> line patients	5%	July 2018 PBAC, item 7.17
I.	Incremental cost of replacing second line nivolumab	\$ [REDACTED]	Cost of a treatment course of pembrolizumab+ platinum + pemetrexed (\$ [REDACTED]) less the cost of a treatment course with nivolumab (\$ [REDACTED])
J.	Incremental cost of new first line	\$ [REDACTED]	Paragraph 6.56
K.	Incremental cost of pembrolizumab+platinum+pemetrexed replacing pembrolizumab monotherapy	-\$ [REDACTED]	Cost of a treatment course of pembrolizumab+ platinum+pemetrexed (\$ [REDACTED]) less the cost of a treatment course with pembrolizumab monotherapy (\$ [REDACTED])

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**Table 20: Estimated use and financial implications: patient numbers and incremental cost: Department of Health calculations**

		2020	2021	2022	2023	Calculation
<b>Patients</b>						
1.	Agreed second line nivolumab patients	████	████	████	████	Deed
2.	NSQ, EGFR ALK ROS negative	████	████	████	████	1.x D.
3.	PD-L1 > 50%, NSQ, EGFR ALK	████	████	████	████	1.x F.
4.	Second line nivolumab replacements	████	████	████	████	2. – 3.
5.	New first line patients	████	████	████	████	4. x H.
6.	Pembrolizumab+ platinum +pemetrexed+ replacing pembrolizumab monotherapy	████	████	████	████	3. x G. x H.
	Total treated patients	████	████	████	████	4.+5.+6.
<b>Incremental cost</b>						
7.	Second line nivolumab replacements	-\$ █████	-\$ █████	-\$ █████	-\$ █████	4.x I
8.	New first line patients	-\$ █████	-\$ █████	-\$ █████	-\$ █████	5. x J.
9.	Pembrolizumab+ platinum +pemetrexed replacing pembrolizumab monotherapy	-\$ █████	-\$ █████	-\$ █████	-\$ █████	6.x K
	Total incremental cost	-\$ █████	-\$ █████	-\$ █████	-\$ █████	

Source: Department of Health

The redacted table shows that the estimated number of patients by 2023 would be less than 10,000 and ICERS would in the range of more than \$200,000/QALY.

**Table 21: Estimated use and financial implications: patient numbers and incremental cost: resubmission patient numbers**

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Source
<b>Patients</b>								
1.	Patients that would have been treated with comparator - offset with nivolumab	████	████	████	████	████	████	B51 to G51, Net Cost to PBS worksheet
2.	Patients that would have been treated with comparator - not offset	██	██	██	██	██	██	B49 to G49 minus B51 to G51, Net Cost to PBS worksheet
3.	Patients that would not have been treated with comparator (i.e., new patients) - not offset	██	██	██	██	██	██	B25 to G365, Epidemiology and Patient Number worksheet

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4.	Patients that would have been treated with pembrolizumab monotherapy	■	■	■	■	■	■	J25 to O25, Epidemiology and Patient Number worksheet
5.	Total treated patients	■	■	■	■	■	■	B45 to G45, Epidemiology and Patient Number worksheet
<b>Incremental cost</b>								
	Patients that would have been treated with comparator - offset with nivolumab	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	1. x I in Table 19
	Patients that would have been treated with comparator - not offset	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	2. x J in Table 19
	Patients that would not have been treated with comparator (i.e., new patients) - not offset	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	3. x J in Table 19
	Patients that would have been treated with pembrolizumab monotherapy	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■	4. x K in Table 19
	<b>Total incremental cost</b>	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	

\* The resubmission included less than 10,000 grandfathered patients in Year 1  
Source: Pembrolizumab\_1L NSCLC KN-189\_Budget Impact Model\_March 2019.xls provide with the resubmission

The redacted table shows that the estimated number of patients at year 6 would be less than 10,000, and ICERs would be in the range of \$15,000/QALY - \$45,000/QALY.

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

- 6.67 The resubmission stated that the sponsor agrees to enter into an agreement on sharing the costs of the Commonwealth subsidy for supply of pembrolizumab in combination with pemetrexed and carboplatin/cisplatin for the treatment of NSCLC in patients whose tumours are non-squamous, EGFR wildtype and ALK translocation and ROS-1 negative. The agreement proposed included a SPA for pembrolizumab as well as annual subsidisation caps where the sponsor agrees to reimburse a proportion of any costs above the subsidisation caps to the Commonwealth.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of pembrolizumab, to be used in combination with platinum chemotherapy and pemetrexed, on the basis that it should be available only under special arrangements under section 100 – Efficient Funding of Chemotherapy. The PBAC recommended the listing be made available for the treatment of patients with Stage IV NSQ NSCLC, who are EGFR wild type, and negative for ALK or ROS1 gene rearrangements, under the circumstances shown in the table in Section 8 below. The PBAC considered a small (around 5%) reduction in the weighted price proposed in the PSCR was required to address the outstanding uncertainties regarding the cost effectiveness of pembrolizumab+platinum+pemetrexed, regardless of PD-L1 status.
- 7.2 For patients with PD-L1 TPS<50%, the PBAC is satisfied that pembrolizumab used in combination with platinum chemotherapy and pemetrexed provides, for some patients, a significant improvement in efficacy over platinum doublet chemotherapy followed by a PD-(L)1 inhibitor.
- 7.3 For patients with PD-L1 TPS≥50%, the PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of pembrolizumab used in combination with platinum chemotherapy and pemetrexed would be acceptable at the pembrolizumab price proposed in the PSCR for this population, noting that the cost per patient per treatment course was similar to that of alternative therapies including pembrolizumab monotherapy. However, the PBAC considered there was some residual uncertainty which could be addressed by a further small reduction in the weighted price.
- 7.4 The PBAC considered the resubmission's nominated comparators for the PD-L1 TPS<50% population and the PD-L1 TPS≥50% population were appropriate (paragraph 5.1). The PBAC also recalled that it had recommended the listing of ABCP at its March 2019 meeting and the resubmission appropriately nominated it as a near-term comparator. The PBAC noted that ABCP was not listed on the PBS at the time of its consideration.
- 7.5 For patients with PD-L1 TPS <50%, the PBAC considered the subgroup analysis of

KN189 was reasonable and supported the clinical claim. The PBAC agreed with the resubmission's claim, noting the substantial and clinically relevant improvement shown in the more mature data presented in the resubmission (Table 7), as well as the new information about the extent of subsequent PD-(L)1 inhibitor use post-progression, which addressed its previous concerns (see paragraph 6.30).

- 7.6 For patients with PD-L1 TPS  $\geq 50\%$ , the indirect comparison presented relied on the use of multiple subgroups to ensure a comparison based on similar patients. The PBAC noted that the PFS HR, but not the OS HR, was statistically significant in favour of pembrolizumab+platinum+pemetrexed over pembrolizumab monotherapy. Moreover, the PBAC recalled its previous view that an indirect comparison relying upon subgroups from each trial was inherently uncertain, and it considered the resubmission did not adequately address the range of transitivity and methodological issues introduced with this comparison (see paragraphs 6.34 and 6.35). Overall, the PBAC considered that the evidence did not support a conclusion of superiority. However, the PBAC further considered that from the evidence provided it was unlikely that pembrolizumab+platinum+pemetrexed was inferior to pembrolizumab monotherapy in terms of effectiveness.
- 7.7 The PBAC reaffirmed its view that a claim of inferior safety to the nominated comparators in paragraph 5.1 was reasonable.
- 7.8 The PBAC considered that, in patients with PD-L1 TPS  $\geq 50\%$ , pembrolizumab used in combination with platinum chemotherapy and pemetrexed may provide, for a small group of patients, an improvement in efficacy that outweighs the additional toxicity compared with pembrolizumab monotherapy.
- 7.9 The PBAC also noted the naïve indirect comparison between pembrolizumab+platinum+pemetrexed and ABCP (KN189 and IMpower 150), and the NMA presented in support of this comparison. The PBAC considered this comparison largely uninformative given: the naïve nature of the analysis; the fact that the resubmission did not assess the range of potential differences between the trials; and that substantial new information regarding the NMA was provided with the PSCR and was unable to be evaluated.
- 7.10 For the PD-L1 TPS  $< 50\%$  subgroup, the PBAC considered that the updates to the economic model largely addressed its major concerns with the previous model (paragraph 6.45). However, the PBAC agreed with the ESC concerning the validity and appropriateness of the utilities (paragraph 6.51) and considered the ICER was likely to be higher than the base case presented in the resubmission.
- 7.11 For the PD-L1 TPS  $\geq 50\%$  subgroup, the PBAC maintained that a cost utility analysis was not appropriate given the issues discussed in paragraph 7.6. However, the PBAC noted that with the price reduction offered in the PSCR for this subgroup, the cost per patient per treatment course for pembrolizumab+platinum+pemetrexed (\$██████) and pembrolizumab monotherapy (\$██████) were similar, albeit remained higher for the

combination treatment.

- 7.12 The PBAC advised that a small (around █%) price reduction in the pembrolizumab weighted price per vial would address the outstanding uncertainties raised in paragraph 7.10 and 7.11.
- 7.13 The PBAC considered the financial estimates provided in the resubmission would need to be revised to incorporate (i) the net financial implications for the health budget (including costs to MBS and the Department of Human Services) (ii) revised patients numbers as discussed in paragraph 7.14 and iii) costs for grandfathered patients using the approach outlined in paragraph 6.67. The PBAC noted the revised financial estimates should be in the format required by Section 4 of the PBAC Guidelines.
- 7.14 The PBAC considered the listing would require a modest expansion of the existing risk sharing arrangements (RSA) for PD-(L)1 inhibitors. The PBAC noted the Department of Health methodology for determining the incremental cost of pembrolizumab was consistent with that previously accepted by the sponsor and considered it was appropriate to use this methodology for determining the proposed expansion of the RSA. The PBAC also considered the Department's approach to estimating patient numbers should be used to progress this listing in line with Table 20, and that this was consistent with previous advice. The PBAC noted the financial implications should ABCP or any other PD-(L)1 inhibitor be listed on the PBS for NSCLC before the expenditure caps are finalised will need to be considered.
- 7.15 The PBAC noted the following regarding the restriction criteria:
- The requested continuation listing required patients to continue pembrolizumab in combination with pemetrexed. However, the PBAC noted that the KN-189 protocol allowed discontinuation of chemotherapy (or pembrolizumab) if there was unacceptable toxicity. Therefore, the PBAC considered it appropriate that the PBS continuing criteria allow patients to discontinue pemetrexed if there was unacceptable toxicity.
  - The initial criteria included "The patient must not have received prior systemic treatment for this condition in the metastatic setting" which is different to the wording currently included for the pembrolizumab monotherapy setting which states, "The patient must not have previously been treated for this condition in the metastatic setting". The PBAC considered the restriction wording should be consistent with the wording that is currently included in the pembrolizumab monotherapy listing.

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- The criteria included “The patient may only receive one course of anti-PD-(L)1 treatment in their lifetime for this condition”. The PBAC recalled it had previously advised that the proposed restriction of pembrolizumab monotherapy as a first-line therapy for metastatic NSCLC and the restriction of nivolumab and atezolizumab as second-line therapies for the same indication included sufficient provisions to ensure that the PBS does not subsidise sequential immunotherapy for NSCLC (paragraph 6.10, pembrolizumab PSD, July 2018 PBAC meeting). The PBAC noted that should any PD-(L)1 inhibitors be listed in an earlier disease stage, additional restriction wording for all PD-(L)1 inhibitors may be warranted.
- 7.16 The PBAC found that the criteria prescribed by the *National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for pembrolizumab in combination with platinum chemotherapy and pemetrexed:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over the nominated comparators in terms of overall survival in the PD-L1 TPS <50% patient population;
  - b) The treatment is expected to address a high and urgent unmet clinical need as there are currently no immunotherapies listed on the PBS for the first-line treatment of NSCLC patients with TPS<50%; and
  - c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
- 7.17 The PBAC advised that, under subsection 101(3BA) of the *National Health Act 1953*, this listing for pembrolizumab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.18 The PBAC reaffirmed its advice that pembrolizumab for NSCLC is not suitable for prescribing by nurse practitioners (paragraph 6.13, 7.17 pembrolizumab PSD, July 2018).
- 7.19 The PBAC advised that the Early Supply Rule should not apply to this listing of pembrolizumab.
- 7.20 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Amend existing listing as follows:

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer	
PEMBROLIZUMAB 100 mg/4 mL injection, 4 mL vial	200 mg	3	Keytruda®	MK

<b>Category / Program:</b>	Section 100 – Efficient Funding of Chemotherapy
<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>Episodicity:</b>	-
<b>Severity:</b>	Stage IV (metastatic)
<b>Condition:</b>	non-small cell lung cancer
<b>PBS Indication:</b>	Stage IV (metastatic) non-small cell lung cancer
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	-
<b>Clinical criteria:</b>	Patient must not have previously been treated for this condition in the metastatic setting, AND The condition must be non-squamous type non-small cell lung cancer, AND The treatment must be in combination with pemetrexed, AND The treatment must be in combination with carboplatin; OR The treatment must be in combination with cisplatin AND The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement or a c-ROS proto-oncogene 1 (ROS1) gene rearrangement in tumour material AND Patient must have a WHO performance status score of 0 or 1.
<b>Population criteria:</b>	-
<b>Prescriber Instructions:</b>	-
<b>Administrative Advice:</b>	No increase in the maximum number of repeats will be authorised. No increase in the maximum quantity or number of units may be authorised  In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.  Special pricing arrangements apply

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Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer	
PEMBROLIZUMAB 100 mg/4 mL injection, 4 mL vial	200 mg	6	Keytruda®	MK

<b>Category / Program:</b>	Section 100 – Efficient Funding of Chemotherapy
<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>Episodicity:</b>	-
<b>Severity:</b>	Stage IV (metastatic)
<b>Condition:</b>	non-small cell lung cancer
<b>PBS Indication:</b>	Stage IV (metastatic) non-small cell lung cancer
<b>Treatment phase:</b>	Continuing
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	-
<b>Clinical criteria:</b>	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have developed disease progression while being treated with this drug for this condition, AND The treatment must be in combination with pemetrexed, unless the patient has experienced drug toxicity.
<b>Population criteria:</b>	-
<b>Prescriber Instructions:</b>	The treatment with this drug must not exceed a lifetime maximum of 24 months' therapy.
<b>Administrative Advice:</b>	No increase in the maximum number of repeats will be authorised. No increase in the maximum quantity or number of units may be authorised.  In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.  Special pricing arrangements apply

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Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer	
PEMBROLIZUMAB 100 mg/4 mL injection, 4 mL vial	200 mg	2	Keytruda®	MK

<b>Category / Program:</b>	Section 100 – Efficient Funding of Chemotherapy
<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>Episodicity:</b>	-
<b>Severity:</b>	Stage IV (metastatic)
<b>Condition:</b>	Non-small cell lung cancer
<b>PBS Indication:</b>	Stage IV (metastatic) non-small cell lung cancer
<b>Treatment phase:</b>	Grandfathering
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	-
<b>Clinical criteria:</b>	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date], AND Patient must not have previously been treated for this condition in the metastatic setting at the time non-PBS subsidised treatment with this drug for this condition was initiated, AND The condition must be non-squamous type non-small cell lung cancer, AND Patient must have had a WHO performance status of 0 or 1 at the time non-PBS subsidised treatment with this drug for this condition was initiated, AND Patient must not have developed disease progression while being treated with this drug for this condition, AND The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement or a c-ROS proto-oncogene 1 (ROS1) gene rearrangement in tumour material
<b>Prescriber Instructions:</b>	A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
<b>Administrative Advice:</b>	No increase in the maximum number of repeats will be authorised. No increase in the maximum quantity or number of units may be authorised.  In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. Special pricing arrangements apply

## 9 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.

## **10 Sponsor's Comment**

The sponsor had no comment.