

4.07 PEMBROLIZUMAB

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

1 Purpose of Application

- 1.1 The minor resubmission requested a Section 100 (Efficient Funding of Chemotherapy) (S100 EFC) Authority Required (Streamlined) listing of pembrolizumab for the first-line treatment of patients with metastatic (Stage IV) non-small cell lung cancer (NSCLC), whose tumours do not have an activating epidermal growth factor receptor (EGFR) gene mutation or an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, and whose tumours express high levels of programmed cell death ligand 1 (PD-L1), defined as a tumour proportion score (TPS) of $\geq 50\%$.
- 1.2 The minor resubmission stated that the Medical Services Advisory Committee (MSAC) has endorsed use of PD-L1 testing for eligibility to pembrolizumab and that its final ratification is expected following a positive PBAC recommendation.

2 Requested listing

- 2.1 The requested PBS listings are shown below. The minor resubmission requested a Special Pricing Arrangement (SPA). Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Proposed PBS Listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
PEMBROLIZUMAB			Published price:	Keytruda [®] Merck Sharp & Dohme (AU) Pty Ltd
50 mg injection: powder for, 1 vial ^a	200 mg	5 6 (initial) ^a	\$9,023.83 (public) ^b	
100 mg/4 mL injection, 1 vial ^a		7 6 (continuing)	\$9,187.35 (private) ^b	
			Effective price: \$ [REDACTED] (public) ^b \$ [REDACTED] (private) ^b	

Treatment phase: Initial treatment

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IV (metastatic) previously untreated
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) previously untreated non-small cell lung cancer

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Treatment phase:	Initial
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The condition must be previously untreated Patient must not have been treated for this condition in the metastatic setting, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have a WHO performance status score of 0 or 1, AND The treatment must not exceed a total of 6 7 doses at a maximum dose of 200 mg every 3 weeks.</p>
Population criteria:	<p>Patient must have evidence of programmed cell death ligand 1 (PD-L1) expression in at least 50% of tumour cells in the tumour sample, AND Patient must have no evidence of an activating epidermal growth factor receptor (EGFR) gene or of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.</p>
Administrative Advice	<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 arrangements apply.</p>

^a Both for initial treatment and continuing treatment

^b The dispensed prices have been recalculated using the Efficient Funding of Chemotherapy (EFC) fees as updated in July 2017.

^c Prices related to proposed special price arrangement

Treatment phase: Grandfathering

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IV (metastatic) previously untreated
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) previously untreated non-small cell lung cancer
Treatment phase:	Initial
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have stable or responding disease, AND The treatment must be the sole PBS-subsidised therapy for this condition,</p>

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	<p>AND Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to (date of listing),</p> <p>AND Patient must have had a WHO performance status of 0 or 1 at the time of treatment initiation,</p> <p>AND The treatment must not exceed a total of 6 doses at a maximum dose of 200 mg every 3 weeks.</p>
Population criteria:	<p>Patient must have evidence of programmed cell death ligand 1 (PD-L1) expression in at least 50% of tumour cells in the tumour sample,</p> <p>AND Patient must have no evidence of an activating epidermal growth factor receptor (EGFR) gene or of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.</p>
Administrative Advice	<p><i>No increase in the maximum number of repeats will be authorised.</i></p> <p>In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.</p> <p>Special Pricing Arrangements apply.</p>

Treatment phase: Continuing treatment

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

- 2.2 The pre-PBAC response stated that the sponsor did not agree to include the criterion for performance status in the grandfathering restriction. The PBAC noted that this criterion was included in the sponsor's proposed wording for the grandfathering restriction and confirmed that it would be necessary to include a criterion for performance status in the grandfathering restriction. The pre-PBAC response agreed with all other changes to the restriction as proposed by the Secretariat.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Background

Registration Status

- 3.1 In March 2017, pembrolizumab was approved by the TGA for the treatment of previously untreated metastatic NSCLC patients with tumours that are PD-L1 TPS $\geq 50\%$ (as determined by a validated test), EGFR wildtype and ALK translocation negative.
- 3.2 Other TGA-approved indications include:
- advanced NSCLC whose tumours express PD-L1 with a $\geq 1\%$ TPS (as determined by a validated test) and who have received platinum-containing chemotherapy
 - unresectable or metastatic melanoma in adults, as monotherapy
 - recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy
 - monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin Lymphoma following autologous stem cell transplant or at least two prior therapies
 - locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy or are not eligible for cisplatin-containing therapy.

Previous PBAC considerations

- 3.3 This was the third submission to the PBAC for pembrolizumab for the first-line treatment of NSCLC in patients whose tumour express PD-L1 at TPS $\geq 50\%$. The first two PBAC submissions were part of integrated codependent submissions considered in March and November 2017.
- 3.4 Pembrolizumab is currently listed on the PBS for unresectable Stage III or Stage IV malignant melanoma, regardless of PD-L1 expression.
- 3.5 At the March 2017 PBAC meeting, an integrated codependent submission to list pembrolizumab as first-line treatment for patients with Stage IIIB/IV, PD-L1 TPS $\geq 50\%$ NSCLC was rejected by the PBAC on the basis of unfavourable and uncertain cost-effectiveness. The PBAC also advised that there was uncertainty in selecting a PD-L1 expression threshold to define an optimal patient population mostly likely to respond to treatment (Item 6.04, public summary document (PSD), March 2017).

- 3.6 At the November 2017 PBAC meeting, the integrated codependent resubmission for pembrolizumab as first-line treatment for patients with Stage IV, PD-L1 TPS \geq 50% NSCLC was deferred by the PBAC. In deciding to defer, the PBAC advised that (i) a further price reduction would be required for acceptable cost effectiveness once necessary changes are made to the economic evaluation; (ii) negotiations with the sponsor are required to determine the best approach for a Risk Sharing Agreement (RSA) in the context of the existing RSA for nivolumab in NSCLC; and (iii) updated advice is needed from MSAC in relation to the codependent PD-L1 test. The PBAC also advised that, if MSAC subsequently decided to support the MBS listing for PD-L1, it would support the listing of pembrolizumab according to the circumstances supported by MSAC, once the PBAC's other concerns were resolved (paragraph 7.1, pembrolizumab November 2017 PBAC PSD).
- 3.7 The minor resubmission stated that MSAC has endorsed use of PD-L1 testing for eligibility to pembrolizumab and that its final ratification is expected following a positive PBAC recommendation.

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

- 4.1 The minor resubmission did not change the main comparator nominated in the March and November 2017 codependent submissions: no test and treatment with platinum-based doublet chemotherapy for all patients. The PBAC previously accepted platinum-based doublet chemotherapy as the appropriate comparator for pembrolizumab, however, considered that pembrolizumab may displace, not replace, use of platinum-based doublet chemotherapy in the proposed target population (paragraph 7.5, pembrolizumab November 2017 PSD).

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item.

Consumer comments

- 5.2 The PBAC noted and welcomed the input from individuals (4), health care professionals (3) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with pembrolizumab, including fewer side effects and achieving better control of NSCLC, compared to chemotherapy. The comment supported the PBS listing of pembrolizumab for NSCLC in patients with TPS \geq 50%.
- 5.3 The PBAC noted the letter from the Lung Foundation Australia, which provided epidemiological data on lung cancer and a patient account of the experience with

pembrolizumab treatment. The Lung Foundation Australia described the benefits of treatment with pembrolizumab and expressed support for its PBS listing.

- 5.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the minor resubmission, on the basis of increased PFS and OS benefit and decreased toxicity compared to platinum-based doublet chemotherapy. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) in this context as being 5 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on the KN-024 trial.

Economic analysis

- 5.5 In the November 2017 major resubmission, a cost-effectiveness analysis and cost-utility analysis was presented, based on the claim of superior effectiveness and safety of pembrolizumab compared to platinum-based doublet chemotherapy in treatment-naïve NSCLC patients whose tumours expressed high levels of PD-L1 (TPS ≥50%). The basic structure of the economic model was unchanged from the March 2017 submission, which the PBAC considered was sound.
- 5.6 The minor resubmission did not alter the economic model structure from March/November 2017, however it presented a respecified model. The main changes in the model variables/assumptions in the minor resubmission and remaining economic issues from the November 2017 major resubmission are summarised below.

Table 1: Comparison of the elements of the economic model in the November 2017 major resubmission and the March 2018 minor resubmission

Model variable	November 2017		March 2018 minor resubmission
	Major resubmission	PBAC comments	
Use of Kaplan-Meier trial data	<p>KM estimates from KN-024 were used up to a certain time point, after which the start point of the goodness of fit comparison for the extrapolation was determined by the post hoc use of the Chow test:</p> <p>PFS: week 27 OS: pembrolizumab: week 32; chemotherapy: week 40</p> <p>The resubmission provided OS data with a median follow up of 19 months, which was updated to 25 months in the revised model</p>	<p>The PBAC considered that use of the Chow test was inappropriate and added a source of uncertainty to the modelled results. The PBAC advised that the base case of the economic model would need to be respecified to use the observed KM results from the key trial in the model up to the median duration of follow-up.</p> <p>The PBAC considered that the trial data was robust, however considered that the OS data in the final analysis supplied in the PSCR remained immature to estimate reliably the magnitude of long-term</p>	<p>The minor resubmission stated that the model used KM results up to the median duration of follow up of 97 weeks. The start point of the goodness of fit comparison for the extrapolation is:</p> <p>PFS: week 9 OS: week zero</p> <p>The minor resubmission stated that the first radiologic tumour response assessment was performed at week 9 in KN-024, and that, as data were not available prior to week 9, parametric functions were fitted from week 9 onwards for PFS. However, the workbook provided with the minor resubmission showed that PFS data were available</p>

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

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	accompanying the PSCR.	survival benefits of pembrolizumab.	prior to week 9. Approximately a third of patients were observed to have progressed by week 9. The exclusion of KM results prior to week 9 is inconsistent with the PBAC's advice and does not appear to be adequately justified. A distinction may have to be drawn between when the event occurred, and when the event was confirmed (ie a progression event confirmed not to be a pseudo-progression event).
Extrapolation	PFS: Pembrolizumab: exponential Chemotherapy: Weibull OS: Pembrolizumab: log-logistic Chemotherapy: exponential	The PBAC advised that the base case of the economic model would need to be respecified to apply: <ul style="list-style-type: none"> • the same extrapolation function between treatment arms for both PFS and OS; • a conservative set of extrapolation curves after the median duration of follow-up that take into account the remaining uncertainty in the magnitude of PFS and OS benefit. 	PFS: exponential (both arms) OS: exponential (both arms)
Convergence	No convergence of modelled survival curves.	The PBAC advised that the base case of the economic model would need to converge the extrapolation curves to the base case time horizon of 7.5 years.	From year 5 (week 260) a proportional adjustment was made to the survival probabilities, to converge the modelled curves at 7.5 years (week 390).
Drug acquisition costs	Based on the proposed price for pembrolizumab and the PBS listed prices for chemotherapies at the time of the resubmission.	The PBAC considered that a further price reduction was required for any PBS listing of pembrolizumab to be acceptably cost-effective.	Rather than a price reduction, a █% rebate on the pembrolizumab cost was applied (█).
Remaining issues	November 2017		March 2018 minor resubmission
	Major resubmission	PBAC comments	
Cost of second-line nivolumab	The resubmission assumed that patients would receive █ 2-week cycles (approximately █ months) of nivolumab treatment after they have failed first-line platinum-based doublet chemotherapy, based on the nivolumab November 2016 PSD. The ESCs considered that the duration of second-line nivolumab following first-line platinum-based doublet chemotherapy was overestimated.	The PBAC advised that the base case of the economic model would need to be respecified to: <ul style="list-style-type: none"> • estimate the duration of post-chemotherapy nivolumab use following the approach advised by the ESCs; and • incorporate the effective price of nivolumab (in the case where pembrolizumab receives a positive PBAC recommendation so that the Deed of Agreement for nivolumab can then be disclosed to the sponsor of pembrolizumab). 	The minor resubmission stated that the sponsor agrees to incorporate the effective price of nivolumab if pembrolizumab receives a positive recommendation. However, the minor resubmission argued that the ESCs' approach of using median PFS2 – median PFS1 as the basis for the nivolumab treatment duration is not accurate, and so maintained the same approach to calculating the nivolumab treatment duration as per the November 2017 major resubmission. The arguments were: <ul style="list-style-type: none"> • PFS2 was defined in KN-024 from an ITT perspective as including progression events (including deaths)

			<p>occurring before initiation of second-line therapy, thus shortening the time period from randomisation to PFS2 event compared to a definition which only include progression events occurring after initiation of second-line therapy. This is reasonable.</p> <ul style="list-style-type: none"> • The mean is preferred to the median when estimating length of treatment and the truncated mean, which underestimates the overall mean, is a conservative approach when estimating cost offsets. This is reasonable. • Treatment duration would be longer in patients whose NSCLC tumours strongly express PD-L1, supported by observational data from a US post-market database. This depends on whether it is accepted that PD-L1 status predicts treatment effect variation consistently across nivolumab and pembrolizumab, and thus a longer duration for second-line nivolumab treatment is reasonable for this subgroup compared to all patients who receive PBS-subsidised nivolumab in second-line NSCLC.
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Abbreviations: KM=Kaplan-Meier; PSCR=pre-Subcommittee Response

- 5.7 The KM data are the same in the workbook accompanying the November 2017 PSCR and the current minor resubmission. However, the PSCR stated that the median follow up was 25.2 months, whereas the minor resubmission stated that the median follow-up was 97 weeks (i.e. 22.4 months). Without the Clinical Study Report for the final analysis of KN-024 it was not clear during the evaluation which was correct. The pre-PBAC response following the minor resubmission stated that, “data included in the economic model had a median follow-up of 25.2 months (107 weeks). Kaplan-Meier curves to 97 weeks were used because the data are too sparse beyond 97 weeks for stable estimation across modelled outcomes.”
- 5.8 Verification of the stepped economic analyses conducted by the minor resubmission is presented below.

Table 2: Revised stepped economic analyses

Parameter	ICER
Base case ICER presented in the November 2017 PSCR, with pembrolizumab cost \$ [REDACTED] per 50 mg vial.	\$ [REDACTED]
Minor resubmission changes	
Extrapolations using the full sets of observed data. This analysis does not use observed KM data in the model, rather these reflect parametric models fitted to all observed data.	\$ [REDACTED]
KM curves to median duration of follow-up. Observed PFS and OS KM data are used until week 97, with extrapolation beyond week 97 based on all observed data. For PFS, the extrapolation was based only on data after week 9; the observed data approaching week 97 may not be reliable. However, holding all other aspects constant, the model is not sensitive to changing the time point from which extrapolated data were used (extrapolation from time points ^a closer to median PFS increases the ICER slightly to \$ [REDACTED]).	\$ [REDACTED]
Conservative set of extrapolation curves for OS (exponential). The exponential model was the best fitting model (according to AIC/BIC) to all of the observed data. However, the assessment of which set of extrapolated curves was the most conservative would have been assisted by traces of the area between the pembrolizumab and SOC OS curves for each extrapolation type. Visual inspection of Figure 2 is insufficient to draw a clear conclusion.	\$ [REDACTED]
Conservative set of extrapolation curves for PFS (exponential). According to the AIC/BIC, the best fitting models were not used in this step, where Weibull may be more appropriate for pembrolizumab; and the exponential model may be more appropriate for the SOC arm. However this has only a minor effect on the ICER (reducing to \$ [REDACTED]). However, the assessment of which set of extrapolated curves was the most conservative would have been assisted by traces of the area between the pembrolizumab and SOC PFS curves for each extrapolation type. Visual inspection of Figure 1 is insufficient to draw a clear conclusion.	Unchanged
Apply the same extrapolation function between treatment arms. The parametric model for SOC PFS was changed from Weibull to exponential, for consistency with the pembrolizumab PFS arm. Selecting a Weibull distribution to extrapolate both PFS treatment arms had only a minor effect on the ICER (reducing to \$ [REDACTED]).	\$ [REDACTED]
Converge the curves at 7.5 years. The resubmission assumed that the pembrolizumab PFS and OS curves begin to converge with the SOC PFS and OS curves, respectively, from 5 years, reaching convergence at the model time horizon of 7.5 years. The approach used to model convergence appears reasonable.	\$ [REDACTED]
Apply rebate of [REDACTED] % [REDACTED] The approach used to model the rebate is reasonable.	\$ [REDACTED]

^a Week 55 for pembrolizumab and week 27 for SOC.

ICER=incremental cost effectiveness ratio; KM=Kaplan-Meier; OS=overall survival; PFS=progression free survival; PSCR=Pre-Subcommittee response; SOC=standard of care

Source: Adapted from 'Stepwise Analysis of Changes' worksheet of the 'Section 3 Workbook_Minor Submission FINAL.xlsm' workbook.

The redacted table shows ICERs in the range of \$45,000 - \$75,000.

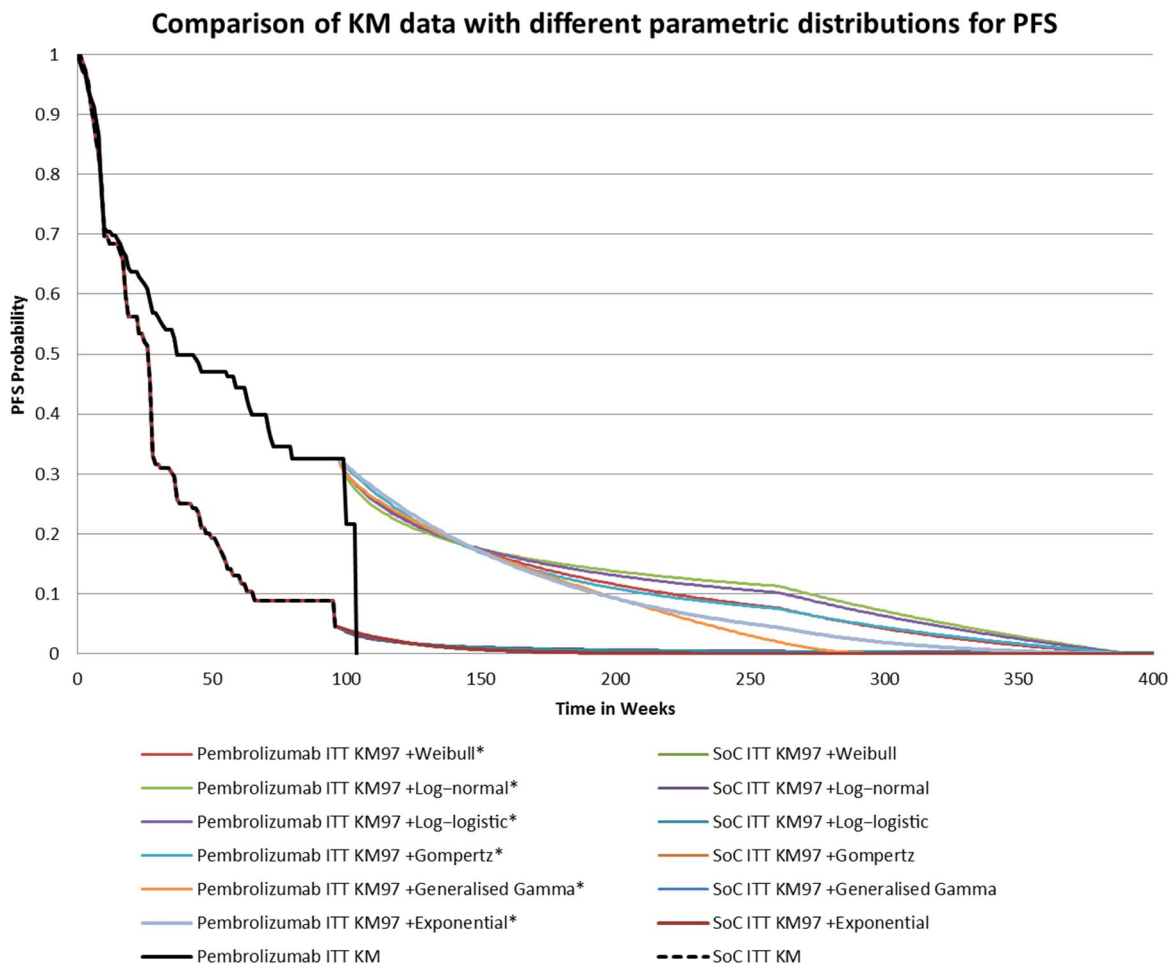
5.9 In relation to the modelling decision to exclude the Kaplan-Meier data from the first 9 weeks when assessing the goodness of fit comparison for the proposed basis of extrapolation beyond the duration of follow-up in the key trial, the pre-PBAC response stated that “the very early decline in the PFS (prior to week 9) was due to early mortality and not a radiologic assessment of progression. The protocol-driven drop of PFS around week 9 made the fitting of parametric curves prior to this time point very challenging in both treatment arms.” It also claimed that, “the model is

not sensitive to the time point for deriving the PFS extrapolations, as later time points had little influence on the ICER”, which the PBAC considered to be irrelevant to the question of whether to exclude earlier data.

5.10 The PBAC noted the explanation provided by the pre-PBAC response regarding the exclusion of data prior to week 9, however considered that it would have been informative if a separate set of extrapolations were fitted to the Kaplan-Meier curves including weeks 0 – 9 in order to examine the consequence of the exclusion. The PBAC concluded that the impact of excluding the first 9 weeks of data on the ICER remained unknown. On this basis, the PBAC considered that the ICER presented by the minor resubmission was uncertain.

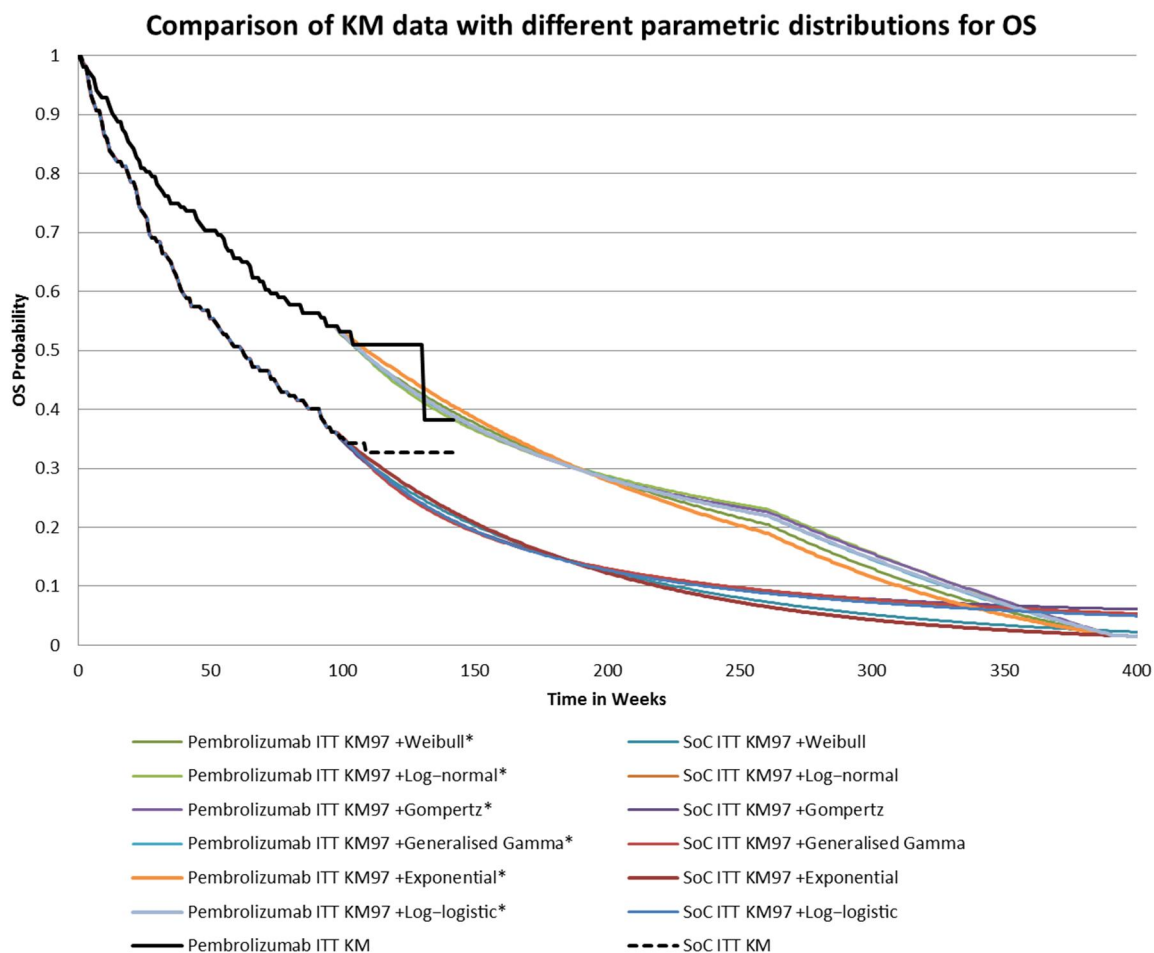
5.11 The trial based PFS and OS curves and the extrapolated curves are presented below.

Figure 1: Kaplan-Meier results and extrapolations (with convergence at 7.5 years) for progression free survival



* The pembrolizumab curves begin to converge towards the SoC (exponential) curve from 5 years (260 weeks). Convergence is achieved at the model time horizon of 7.5 years (390 weeks).

Figure 2: Kaplan-Meier results and extrapolations (with convergence at 7.5 years) for overall survival



* The pembrolizumab curves begin to converge towards the SOC (exponential) curve from 5 years (260 weeks). Convergence is achieved at the model time horizon of 7.5 years (390 weeks).

5.12 The pre-PBAC response stated that the extrapolations for PFS and OS were selected based on the distributions with the most conservative estimates of OS and PFS for the pembrolizumab treatment group. The PBAC considered that, as the pre-PBAC response did not provide traces of the area between the pembrolizumab and SOC curves for each extrapolation type across PFS and OS, it remained uncertain which extrapolations were the most conservative from visual inspection of Figures 1 and 2.

Drug cost/patient/course: \$ [redacted] (reduced by [redacted] % from \$ [redacted] estimated in November 2017, based on an additional rebate)

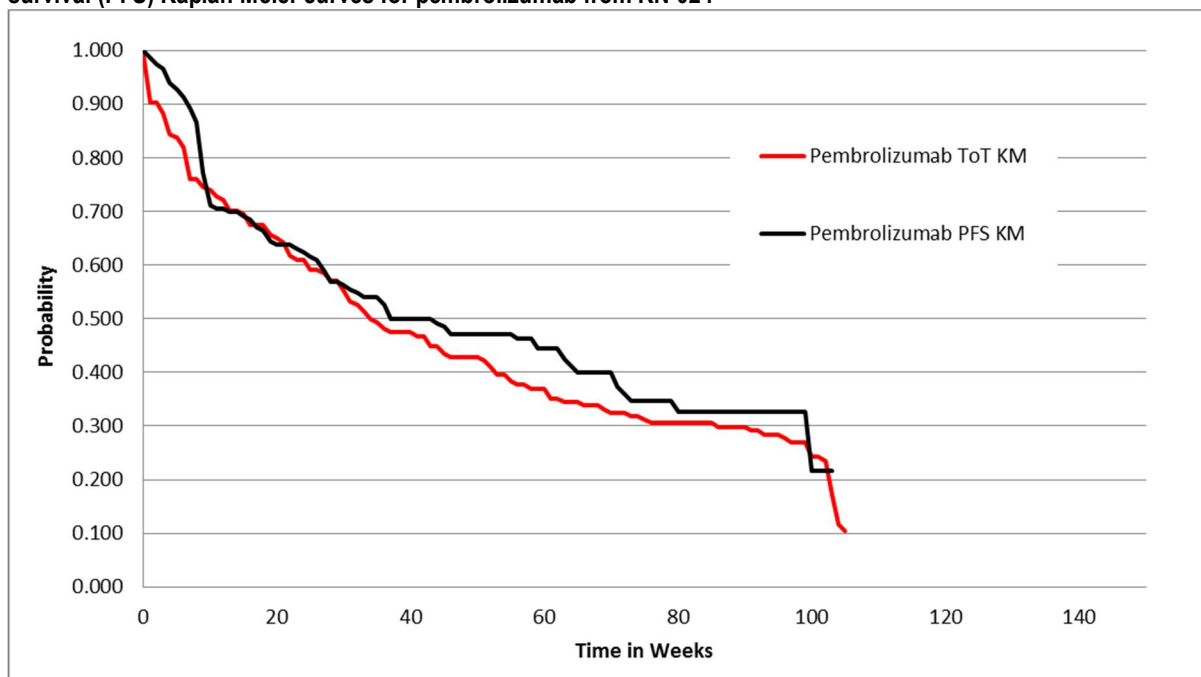
5.13 The minor resubmission stated that, “to establish cost effectiveness, an [redacted] % reduction in the average per patient drug treatment cost (from \$ [redacted] to \$ [redacted]) is being proposed, which would be achieved through an additional rebate that is linked to treatment duration, [redacted]”. Based on the Excel workbook provided with the minor resubmission, the estimated pembrolizumab drug cost per patient per course was \$ [redacted], which

reduced to \$ [REDACTED] with the rebate. Each patient was assumed to require an average of [REDACTED] administrations per course (approximately [REDACTED] weeks), based on the modelled time on treatment (e.g. patients would receive pembrolizumab until they experience disease progression or reach the maximum TGA-approved treatment duration of 2 years), with the proposed rebate coming into effect about halfway between the estimated mean duration of therapy and the maximum approved duration of therapy. The difference in the cost estimates between those given in the minor resubmission and those derived above from the Excel workbook may be due to rounding in calculating the average number of administrations per patient. In the November 2017 major resubmission, the estimated number of pembrolizumab administrations and drug cost per course per patient were [REDACTED] administrations and \$ [REDACTED], respectively².

- 5.14 As the basis of estimating drug cost per patient was based on assuming that time to progression equals time to treatment cessation, the more convincing basis for estimating the cost per patient would have been to use directly reported time to treatment cessation (as per the usual Kaplan-Meier approach), and then, as necessary, extrapolating this more direct measure of treatment duration to thus estimate treatment costs. The figure below shows that, on average, patients in the key trial tended to stop pembrolizumab earlier than they experienced a progression event. As follow-up extended to up to two years, at which time pembrolizumab therapy should be stopped anyway, the drug cost per patient per course using the observed time to treatment cessation from the trial becomes \$ [REDACTED] (based on [REDACTED] administrations at \$ [REDACTED] each), with the [REDACTED]% rebate [REDACTED]). The corresponding ICER/QALY reduces to \$45,000 - \$75,000 from the minor resubmission's base case of \$45,000 - \$75,000.

² The pembrolizumab November 2017 PBAC Minutes stated the medicine cost per patient per course to be \$ [REDACTED], based on an average of [REDACTED] administrations per course (paragraph 6.50). During preparation of the minor overview, it was found that reference to [REDACTED] administrations was made in the pembrolizumab November 2017 major resubmission, however, the economic and financial analyses accompanying the resubmission applied [REDACTED] administrations. Therefore, figures provided in this minor overview have updated those provided in the context of the November 2017 major resubmission.

Figure 3: Comparison of the time to treatment cessation (TOT) Kaplan-Meier curve and the progression free survival (PFS) Kaplan-Meier curves for pembrolizumab from KN-024



- 5.15 In comparison, the drug cost per patient per course for nivolumab for second-line NSCLC is \$ [REDACTED].
- 5.16 At its November 2017 meeting, the PBAC noted that increasing the average per patient cost of pembrolizumab by moving the recommended dose from a 2 mg/kg basis to a fixed 200 mg basis is likely associated with a 25% wastage of pembrolizumab because corroborating evidence indicates that fixed dosing does not improve patient health outcomes. The PBAC recalled that this had contributed to its expectation of a price reduction, given that the TGA has accepted the sponsor’s submission of fixed dosing in the product information (paragraph 7.15, pembrolizumab November 2017 PBAC PSD). At the same meeting in consideration of the major submission for pembrolizumab for urothelial cancer, the PBAC considered that the request for fixed dosing “results in a considerable proportion of patients with urothelial cancer being given a greater dose, at a greater cost, with no evidence of additional benefit. The PBAC therefore considered that it may be reasonable for the price paid for pembrolizumab in urothelial cancer to reflect the cost if weight-based 2 mg/kg dosing was used rather than fixed 200 mg dosing” (paragraph 7.12, pembrolizumab [Item 6.11] November 2017 PBAC PSD).
- 5.17 In a separate minor submission to the March 2018 PBAC meeting, the sponsor has requested changing the PBS listing of pembrolizumab for melanoma from a dose of 2 mg/kg to a fixed dose of 200 mg per dose. This request raised the same issue of wastage about which the PBAC had concerns for pembrolizumab for NSCLC. This separate minor submission conceded that the available evidence indicates that there

is no difference in pembrolizumab efficacy across the dose range of 2 mg/kg to 10 mg/kg.

- 5.18 The pre-PBAC response argued that the TGA approved dose is 200 mg and that no studies have been completed using weight-based dosing. The PBAC noted however, that the separate minor submission for pembrolizumab for melanoma claimed that “there is an essentially flat relationship between pembrolizumab exposure and efficacy or safety within the dose range of 2 to 10 mg/kg”. The PBAC considered that there is no evidence to suggest that these dose-response relationships for pembrolizumab are specific to melanoma. Furthermore, the PBAC recalled its consideration of the pembrolizumab submission for second-line NSCLC at its November 2016 meeting, which requested a weight-based dosing regimen at 2 mg/kg (pembrolizumab [Item 6.05] November 2016 PBAC PSD). The PBAC noted that the sponsor moved to a fixed 200 mg dosing regimen for later pembrolizumab trials across multiple indications, which included first-line NSCLC. However the PBAC noted that no clinical rationale was provided for this change in dosing regimen and therefore considered that the issues of wastage for pembrolizumab in first-line NSCLC remained relevant.

Estimated PBS usage & financial implications

- 5.19 At its November 2017 meeting, the PBAC considered that the submission’s estimates of substantial cost offsets from second-line nivolumab resulting from a PBS listing of first-line pembrolizumab in NSCLC would affect the risk sharing arrangements (RSA) in the Deed of Agreement for nivolumab in NSCLC. The PBAC considered that, if pembrolizumab was made available on the PBS, there would only be a minor increase in the overall number of patients treated for metastatic Stage IV NSCLC either in the first- or second-line setting, above what was accepted for the nivolumab caps at the time of the negotiations with the sponsor of nivolumab. However, as requested, the PBS listing of pembrolizumab would reduce the PBS expenditure on nivolumab, thus reducing the effect of its risk sharing arrangements, without necessarily providing similar risk sharing arrangements across both immunotherapies (paragraph 7.16, pembrolizumab November 2017 PSD).
- 5.20 The minor resubmission maintained the same estimate of patient numbers as in the November 2017 major resubmission, however, presented estimates on the proportion of these patients who would replace the nivolumab (second-line NSCLC) market and the patients who would represent an incremental increase in the overall NSCLC market as a result of the first-line pembrolizumab listing. In approximating the incremental increase in the overall NSCLC market, the minor resubmission presented estimates on the patients who uptake pembrolizumab as a result of changing from first-line chemotherapy, and estimates on the patients who uptake pembrolizumab but would not have received first-line chemotherapy.

5.21 The minor resubmission estimated that 19.53% of the current second-line NSCLC nivolumab market would be replaced by pembrolizumab if it became PBS listed for first-line NSCLC. This was based on the following estimates:

Table 3: Population assumptions and references presented by the minor resubmission

Variable	Value	Source	Comments
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.	<i>This is reasonable (but see para 5.15).</i>
Proportion of NSCLC patients with squamous vs non-squamous histology	22.4% (squamous) 77.6% (non-squamous)	Systemic therapy treatment patterns in patients with advanced non-small cell lung cancer (NSCLC): PivOTAL study. European Journal of Cancer Care, February 2017.	<i>This is reasonable.</i>
Proportion of non-squamous NSCLC patients who are EGFR or ALK negative	= 12.5% (EGFR +ve) + 4% (ALK +ve) = 16.5% total	10-15% of NSCLC patients are estimated to be EGFR positive [Assche et al, "EGFR Mutation Positive Stage IV Non-Small-Cell Lung Cancer: Treatment Beyond Progression", Front Oncol, 2014]. 3-5% of NSCLC patients are estimated to be ALK positive [Crizotinib PSD PBAC November 2013].	<i>This is reasonable.</i>
Prevalence of TPS ≥50%	28.5%	Data on cohort of Australian patients from the KN-024 study.	<i>This is reasonable.</i>
2L nivolumab market replaced by 1L pembrolizumab	19.53%	Calculation = 78.6% x ((77.6% x 83.5%) + 22.4%) x 28.5%	<i>This is reasonable.</i>

5.22 The minor resubmission did not estimate the number of patients who currently receive nivolumab second-line, nor estimate the number of patients that would uptake first-line pembrolizumab using its estimate of the nivolumab market share. However, the economic and financial analyses estimated that nivolumab cost offsets would accrue for 64.2% of patients receiving pembrolizumab. Nivolumab cost offsets were also assumed in 64.2% of grandfathering patients who would have otherwise received first-line chemotherapy.

Table 4: Estimates of numbers and types of patients with Stage IV NSCLC treated with pembrolizumab as presented in the minor resubmission with a comparison of these estimates generated with reference to the economic and financial models of the minor resubmission

Population assumptions		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Patients who switch from chemo to pembro	■	■	■	■	■	■
B	Incremental pembro patients (would not have had chemo)	■	■	■	■	■	■
C1	Grandfathered patients	■	■	■	■	■	■
	Patients who have taken pembro but would not have received chemo	■	■	■	■	■	■
Total pembro patients (A + B + C)		■	■	■	■	■	■
D	Patients for whom a cost offset for nivolumab was generated by the economic and financial models (64.2% of A)	■	■	■	■	■	■
E	Patients who would not have received second-line immunotherapy after progression (A – D)	■	■	■	■	■	■
F	New first-line pembrolizumab population (B + E)	■	■	■	■	■	■
Total pembro patients (D + F)		■	■	■	■	■	■

[REDACTED]

The redacted table shows that at Year 5, the estimated number of patients was less than 10,000 per year.

- 5.23 The “new first-line pembrolizumab population³” proposed by the minor resubmission was defined as the number of patients who were estimated to uptake first-line pembrolizumab, who otherwise would not have received first-line chemotherapy (Row B, Table 4). This population should also include those patients who would have received first-line chemotherapy, but would not have received second-line nivolumab (Row E, Table 4). When these patients are included in “new first-line pembrolizumab population” estimates, they account for approximately half of the estimated number of all patients who would receive first-line pembrolizumab (Row F, Table 4). The pre-PBAC response agreed with the Minor Overview on this approach. However, this is not consistent with the PBAC’s consideration that if pembrolizumab was made available on the PBS, there would only be a minor increase in the overall number of patients treated for metastatic Stage IV NSCLC either in the first- or second-line setting. This is also not consistent with the minor resubmission, which stated that “[the new first-line pembrolizumab population] equates to 23.5% of any new pembrolizumab patients eligible for first line therapy (Years 1 and 2) and increases to 25% (Year 3 onwards)”.
- 5.24 The pre-PBAC response argued that the PBAC’s view “is at odds with the epidemiological estimates presented in the submission, which suggest a substantial increase of at least [REDACTED] new patients.” It further argued that, “unless the estimates are aligned to those proposed in the submission, not all eligible patients would be accommodated”. The pre-PBAC response also presented an alternative approach to determination of new first-line pembrolizumab patients, with different estimates for rows D – F of Table 4, based on assuming 75% rather than 64.2% as the treatment rate with second-line nivolumab for patients initiated on chemotherapy. However, this did not change the total number of pembrolizumab patients proposed by the minor resubmission. The PBAC noted that this alternative approach was not independently verified, but considered that the approach did not ameliorate its primary concerns over the large numbers of patients estimated to be eligible for pembrolizumab.
- 5.25 The minor resubmission also separately presented population and uptake estimates for Stage IIIB/IV patients, “should the PBAC agree that Stage IIIB patients could access treatment with pembrolizumab”. However, the key trial, KN-024, only included patients with Stage IV NSCLC. Furthermore, the TGA product information restricts pembrolizumab treatment to patients with metastatic NSCLC. The PBAC

³ The minor resubmission used this term to define the population of new and additional pembrolizumab patients who currently would not receive either first- or second-line therapy.

considered that there was no justification for broadening the requested access of pembrolizumab to include Stage IIIB patients.

- 5.26 The PBAC noted that the minor resubmission applied a treatment rate for pembrolizumab of 83.5% in Year 1 to 85% in Year 6 of listing, compared to 60% for platinum-based doublet chemotherapy. The PBAC noted that the pre-PBAC response referred to the DUSC advice in relation to the original March 2017 submission, in which DUSC did not change the greater uptake rates for pembrolizumab provided in the pre sub-committee response for that submission. The PBAC also noted the arguments provided in the pre-PBAC response that “this increase in treatment rate is justified given the efficacy and toxicity benefits of pembrolizumab versus standard of care” and that similar treatment uptake rates were accepted in the brentuximab vedotin submission for the treatment of relapsed or refractory CD30+ Hodgkin lymphoma following autologous stem cell transplant. The PBAC considered that this reference to brentuximab vedotin was of no relevance to the estimates of pembrolizumab because it related to a different proposed medicine, with different alternative therapies in a different cancer. However, overall, the PBAC considered that the pembrolizumab treatment uptake rate assumed by the minor resubmission was unrealistically high, given that a proportion of patients may not have tumour material suitable for PD-L1 expression determination and may not meet the performance status requirements specified in the PBS restriction. Further, the PBAC advised that clinicians may choose chemotherapy rather than immunotherapy for a proportion of patients. The PBAC instead advised that a treatment uptake rate of approximately 65% would be more reasonable for pembrolizumab.
- 5.27 The minor resubmission estimated the number of patients to be grandfathered based on the approach in the following table. This did not reflect a known number of patients currently taking pembrolizumab on a compassionate use program, but reflected the proposal in the minor resubmission that the sponsor would create “an early access program (EAP) between the time of a positive PBAC recommendation and the PBS listing date with eligibility criteria being identical to the proposed PBS restriction (March 2018 and August 2018)”. The calculations assume that a full year’s worth of patients would be eligible for pembrolizumab in this seven month period, and that all eligible patients would start pembrolizumab. The minor resubmission did not state what form of subsidy on the published price would be offered in this proposed EAP, which might affect uptake rates.
- 5.28 The pre-PBAC response stated that the sponsor had launched its EAP in February 2018, with eligibility criteria identical to the requested PBS restriction and the costs of pembrolizumab and PD-L1 testing completely subsidised by the sponsor. It stated that 46 patients were enrolled in the first three weeks of the EAP.
- 5.29 The PBAC noted that the minor resubmission included grandfathered patients from the prevalent pool in its epidemiological approach to estimate the size of the PBS population which would be eligible for pembrolizumab. The PBAC considered that this inclusion would affect any proposal to use a risk sharing arrangement to

generate an upper cost per patient for pembrolizumab in order to achieve acceptable cost-effectiveness.

Table 5: Calculation of the number of grandfathered patients in the current minor resubmission

A	Patients available for grandfathering (same in November sub &PSCR and minor resub)		
B	Number of patients that are PD-L1 positive (28.5% × A)		
C	PD-L1+ non-squamous (77.6% × B)		
D	PD-L1+ non-squamous, EGFR- and ALK- (83.5% × C)		
E	PD-L1+ squamous (22.4% × A)		
F	Patients that would have received chemo (60% × (D + E))		
G	Patients that would uptake pembro (83.5% × (D + E))		
H	Therefore, patients who would uptake pembro, who would not uptake chemo (G - F)		

5.30 A comparison of the net cost to the PBS as a result of listing pembrolizumab estimated in the November 2017 Pre-Subcommittee Response (PSCR) and the current minor resubmission is presented below.

Table 6: Comparison of net cost to the PBS as presented in the PSCR to the November 2017 PBAC meeting and in the current minor resubmission and updated with fee changes occurring on 1 January 2018^a

Net cost to PBS	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Nov 2017 PSCR ⁴						
Minor resubmission						
Updated copayment						
Updated EFC fees						
Both updated						

^a The updates do not correct for residual errors in the approach to estimating cost offsets as identified in Section 4.3 of the Commentary to the November 2017 major resubmission. A patient co-payment was erroneously assumed for each comparator medicine administration, rather than per original prescription. This was not corrected for in the minor resubmission, therefore updating the co-payment fees inflates the effect of this difference.

The redacted table shows that at Year 6, the estimated net cost to the PBS would be \$60 - \$100 million.

5.31 The minor resubmission estimated a net cost to the PBS of \$30 – \$60 million in Year 1 of listing, increasing to \$60 - \$100 million per year in Year 6 of listing. Compared to the November 2017 major submission, the minor resubmission estimated a % reduction in the net cost to the PBS over six years. Although the minor resubmission anticipated the number of patients for whom a nivolumab cost offset might be expected, the extent of cost offset per patient is the product of the price of nivolumab multiplied by the duration of therapy

⁴ Table 15 of the pembrolizumab November 2017 PBAC Minutes reported slightly different figures for the net financial implications to the PBS/RPBS. During the preparation of this minor overview, it was found that those figures were based on the November 2017 Commentary. The pembrolizumab PSCR to the November PBAC meeting provided a revised budget impact model, which updated the net PBS estimates in response to that Commentary. The estimates for the net cost to the PBS (for the November 2017 major resubmission) presented in this minor overview are therefore based on the workbook provided with the pembrolizumab November 2017 PSCR, which has been verified to be correct.

of nivolumab. The full details cannot be provided to the sponsor of pembrolizumab until such time as PBAC recommends listing pembrolizumab for NSCLC.

Risk Sharing Arrangement

5.32 The minor resubmission proposed both a special pricing arrangement and a risk sharing arrangement ([REDACTED]).

Further assessments containing Committee in Confidence information

Table 7: Comparison of the minor resubmission’s estimates with the agreed patient numbers in the nivolumab deed

Estimated patient numbers		Calendar years						
Nivolumab (as per estimates for the PBS listing starting 1 August 2017)		1	2	3	4	5	6	–
Squamous		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	–
Non-squamous		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	–
A	Total	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	–
Pembrolizumab (as per minor resubmission)		–	1	2	3	4	5	6
B	Patients for whom a cost offset for nivolumab was generated by the economic and financial models ^a	–	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
C	New first-line pembrolizumab population ^b	–	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
D	Total	–	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Comparison of the minor resubmission’s assumptions with the nivolumab population as per the deed								
E	Minor resubmission’s estimate of proportion of Stage IIIB/IV NSCLC eligible for pembrolizumab ^d	–	19.53%	19.53%	19.53%	19.53%	19.53%	–
F	Pembrolizumab patients with nivolumab offset applied / total nivolumab population (B/A)	–	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	–
G	New pembrolizumab patients/ total nivolumab population (C/A)	–	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	–
H	Extension of Stage IIIB/IV NSCLC population beyond the nivolumab market (C/E)	–	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	–
I	Derived overall eligible population (A + H)	–	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	–
J	Minor resubmission’s estimate of patients with eligible disease ^e	–	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	–

^a Row D of Table 4: 64.2% x patients who switch from first-line chemotherapy to pembrolizumab

^b Row F of Table 4: incremental patients who are treated with pembrolizumab but who would not have had first-line chemotherapy + patients who would not have received second-line immunotherapy after progression

^c [REDACTED] = B + C + [REDACTED] grandfathered patients (who are treated with pembrolizumab but who would not have had first-line chemotherapy)

^d Minor resubmission’s estimate (Table 6, p14) of the proportion of the second-line nivolumab market that would be replaced by pembrolizumab in the first-line setting

^e Based on the minor resubmission’s estimate of patients with advanced (stage IIIB/IV) NSCLC who are candidates for first-line treatment, “Background and assumptions” worksheet of the budget impact model accompanying the minor resubmission

The redacted table shows estimated patient numbers of less than 10,000 per year.

5.33 The table above seeks to assess two sources of patients for pembrolizumab compared to the existing estimates for nivolumab.

- 5.34 The first population is those patients who would no longer receive second-line nivolumab if first-line pembrolizumab was to be listed. As pembrolizumab would be limited to those patients who are not EGFR or ALK positive and whose tumours strongly express PD-L1, the minor resubmission's estimate was that a maximum of 19.53% of the second-line nivolumab population would be replaced by pembrolizumab in the first-line setting (Row E). By comparison, the actual percentages derived from the approach used in the minor resubmission to generate the financial estimates are [REDACTED] (Row F).
- 5.35 The second population is those patients who would not have received second-line nivolumab if first-line pembrolizumab was to be listed (Row C, or Row G as a percentage expansion over the previously agreed nivolumab population). By comparison, the PBAC previously expressed its view that this second population would be small. Specifically, from paragraph 7.16 of the November 2017 PSD: "The PBAC considered that, if pembrolizumab was made available on the PBS, there would only be a minor increase in the overall number of patients treated for metastatic Stage IV NSCLC either in the first- or second-line setting, above what was accepted for the nivolumab caps at the time of the negotiations with the sponsor of nivolumab". Rather, the minor resubmission estimated a substantial increase in the number of NSCLC patients who would be treated with an immunotherapy agent as a result of the proposed first-line listing.
- 5.36 To investigate this further by dividing the minor resubmission's estimates in Row C by 19.53% (the limit of pembrolizumab eligibility to those patients who are not EGFR or ALK positive and whose tumours strongly express PD-L1), it is possible to estimate the total eligible population that the minor resubmission infers would not receive nivolumab (Row H). Adding this estimate to the agreed numbers of nivolumab patients represents [REDACTED] (Row I). This [REDACTED] [REDACTED] the minor resubmission's estimate of the total population with eligible disease (Row J).

Table 8: Sensitivity analyses of the economic evaluation assessing the consequence of different nivolumab cost offsets

Sensitivity analyses of economic evaluation	ICER/QALY
Minor resubmission base case <ul style="list-style-type: none"> • Accept minor resubmission’s estimates of QALYs • Accept minor resubmission’s approach to estimate drug costs (based on PFS rather than ToT) • Assume nivolumab cost offset of \$ [REDACTED] (stated to be from Nivo NSQ NSCLC PSD, Nov 2016) 	\$ [REDACTED]
[REDACTED]	\$ [REDACTED]
Treatment costs based on ToT <ul style="list-style-type: none"> • Accept minor resubmission’s estimates of QALYs • Use ToT to estimate drug costs (rather than PFS) • Assume nivolumab cost offset of \$ [REDACTED] (stated to be from Nivo NSQ NSCLC PSD, Nov 2016) 	\$ [REDACTED]
[REDACTED]	\$ [REDACTED]

5.37 The primary message of the table above is that, [REDACTED]

For more detail on PBAC’s view, see section 6 PBAC outcome.

6 PBAC outcome

6.1 The PBAC deferred making a recommendation to list pembrolizumab for the first line treatment of patients with metastatic (Stage IV) non-small cell lung cancer (NSCLC), who have high expression of programmed cell death ligand 1 (PD-L1), defined as a

tumour proportion score (TPS) of $\geq 50\%$. In deciding to defer, the PBAC advised that its primary concern was that further work was required to determine the size of the patient population eligible for treatment with pembrolizumab. The PBAC also preferred a further price reduction to minimise the indirect, uncertain and delayed reliance on exceeding expenditure caps to achieve cost effectiveness. The PBAC considered that a further reduction in the cost per patient of pembrolizumab might also be required to address the residual uncertainties in the economic evaluation as noted below in paragraphs 6.5 and 6.6. In this context, the PBAC accepted the respecified basis of the economic model to estimate pembrolizumab costs directly from the extrapolated time to treatment cessation. The PBAC noted that this respecification had resulted in the revised ICER of \$45,000/QALY - \$75,000/QALY, compared to the \$45,000/QALY - \$75,000/QALY from the minor resubmission.

- 6.2 The PBAC agreed with the changes to the proposed restriction suggested by the Secretariat, and confirmed that it would be necessary to include a criterion for performance status in the grandfathering restriction. The PBAC foreshadowed that, in the event of any recommendation to list pembrolizumab, as first-line therapy in metastatic NSCLC, both its restriction and that of nivolumab would need to be modified to prevent PBS-subsidised sequential immunotherapy.
- 6.3 The PBAC recalled that, since its first consideration of pembrolizumab for first-line metastatic NSCLC in patients with a TPS of $\geq 50\%$ in March 2017, nivolumab (another PD-L1 inhibitor) has become PBS subsidised for the second-line treatment of NSCLC irrespective of the status of tumour PD-L1 expression. The PBAC confirmed that this had shifted the clinical context and clinical need in the treatment of metastatic NSCLC, as all these patients now had access to immunotherapy in the second-line setting.
- 6.4 The PBAC noted that the ████% rebate offered by the minor resubmission would only apply from 18 months of therapy onwards for a patient receiving pembrolizumab and that this is approximately halfway between the estimated mean duration of therapy and the maximum TGA approved duration of therapy. The PBAC considered that few patients would reach 18 months of treatment. The PBAC also noted the early and sharp decline in the PFS curves following the initiation of pembrolizumab. Notably, this initial decrement in health outcomes was due to early mortality and not radiologic evidence of progression.
- 6.5 The PBAC recalled its advice from the November 2017 meeting that the base case of the economic model would need to be respecified to use the observed Kaplan-Meier results from the key trial in the model up to the median duration of follow-up and to not exclude any Kaplan-Meier results. The PBAC noted that the minor resubmission did not follow its advice for the extrapolation of PFS data and that the first 9 weeks of Kaplan-Meier results for PFS were excluded when assessing the goodness of fit comparison for the proposed basis of extrapolation beyond the duration of follow-up in the key trial. The PBAC noted the explanation provided by the pre-PBAC response regarding the exclusion of data prior to week 9, however considered that it

would have been informative if a separate set of extrapolations were fitted to the Kaplan-Meier curves including weeks 0 – 9 in order to examine the consequence of the exclusion. The PBAC concluded that the impact of excluding the first 9 weeks of data on the ICER remained unknown. On this basis, the PBAC considered that the ICER presented by the minor resubmission remained uncertain.

- 6.6 The PBAC recalled that it had advised that a conservative set of extrapolation curves should be applied after the median duration of follow-up, which take into account the remaining uncertainty in the magnitude of any incremental PFS and OS gains. The PBAC noted that, as the minor resubmission and the pre-PBAC response did not provide traces of the area between the pembrolizumab and SOC curves for each extrapolation option across PFS and OS, it was uncertain which extrapolations were the most conservative. On this basis, the PBAC considered that the ICER presented by the minor resubmission remained uncertain.
- 6.7 The PBAC noted the revised ICER of \$45,000/QALY - \$75,000/QALY retained these two sources of uncertainty, but did estimate the costs of pembrolizumab directly from the observed duration of treatment from the key trial with an appropriate extrapolation.
- 6.8 The PBAC noted that the estimates of the annual numbers of patients treated with pembrolizumab proposed by the minor resubmission relied on an uptake rate of 83.5% in Year 1 increasing to 85% in Year 6 of listing, compared to a constant 60% for platinum-based doublet chemotherapy. The PBAC considered that the pembrolizumab uptake rate assumed by the minor resubmission was unrealistically high, given that a proportion of patients may not have a suitable biopsy and may not meet the performance status requirements specified in the PBS restriction. For the reasons outlined in paragraph 5.26 above, the PBAC considered that an overestimate of the pembrolizumab uptake rate resulted in overestimated financial impact to government. The PBAC instead advised that an uptake rate of approximately 65% would be more reasonable for pembrolizumab.
- 6.9 The PBAC noted that the minor resubmission included grandfathered patients from the prevalent pool in its epidemiological approach to estimate the size of the PBS population which would be eligible for pembrolizumab. The PBAC considered that this inclusion would affect any proposal to use a risk sharing arrangement to generate an upper cost per patient for pembrolizumab in order to achieve acceptable cost-effectiveness.
- 6.10 The PBAC considered that there was a large discrepancy between the estimated patient population proposed by the minor resubmission and the Committee's advice from November 2017 that, if pembrolizumab was made available on the PBS, there would only be a minor increase in the overall number of patients treated for metastatic Stage IV NSCLC either in the first- or second-line setting, above what was accepted for the nivolumab caps at the time of the negotiations with the sponsor of nivolumab. The PBAC considered that the utilisation estimates in Table 4 were within its expectations for the population for whom a cost offset from second-line

nivolumab was estimated, but the committee's concerns centred around the large projected uptake in the added population. The PBAC disagreed with the minor resubmission that such large numbers of patients would be eligible for pembrolizumab but would not subsequently have been eligible for nivolumab. As previously, the PBAC could not identify any clinical rationale for any estimate beyond a small increase for patients who could not tolerate first-line chemotherapy and also be eligible for pembrolizumab. The PBAC was not confident that reducing the uptake rate as advised above would be sufficient to address its concerns with the large projected uptake in the added population. The PBAC was also concerned with the reliability of the overall estimated numbers of patients per year given that the Cancer Drugs Fund Managed Access Agreement in England estimated a similar number of eligible patients per year ([REDACTED]) for an overall population which is about double that of the Australian population.

- 6.11 Overall, the PBAC therefore advised that further work was required to determine the appropriate annual estimates of the overall patient population eligible for treatment with pembrolizumab. The PBAC further suggested that the input of its Drug Utilisation Subcommittee may be required on these estimates.
- 6.12 Given the uncertainty around the estimated extent of utilisation, the PBAC would prefer greater confidence that the cost per patient of pembrolizumab is acceptably cost-effective. The PBAC advised that a further price reduction would help minimise the indirect, uncertain and delayed reliance on exceeding expenditure caps to achieve cost effectiveness. However, the PBAC could not reach a final conclusion on this aspect until the respecified basis of the economic model resulting in a revised ICER of \$45,000/QALY - \$75,000/QALY could be further adjusted to address the residual modelling uncertainties noted in paragraphs 6.5 and 6.6.
- 6.13 In addition, the PBAC also advised that a risk sharing arrangement would also be required to mitigate the overall budgetary risk to Government.

Outcome:

Deferred

7 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.

8 Sponsor's Comment

The sponsor had no comment.