7.17 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 ≥50%.

1.2 An initial minor resubmission lodged on 20 April 2018 was subsequently superseded by a revised minor resubmission lodged on 2 May 2018, including revised spreadsheets dated 26 April 2018 for the "Budget Impact Model" and 2 May 2018 for the "Section 3 Workbook". Wherever the two resubmissions were different, the more recent resubmission was relied upon.

2 Requested listing

2.1 The minor resubmission did not re-present a requested restriction. The requested PBS listings from the previous minor resubmission considered by the PBAC in March 2018, including suggestions and additions proposed by the Secretariat and accepted by the PBAC in March 2018, as well as some minor additions in *italics*, are presented below.

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

Treatment phase: Initial treatment

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives

Severity:	Stage IV (metastatic) previously untreated
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) previously untreated non-small cell lung cancer
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	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 7 doses at a maximum dose of 200 mg every 3 weeks for this condition under this restriction.
Population criteria:	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.
Administrative Advice	No increase in the maximum number of repeats will be authorised. In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. Special pricing arrangements apply.

[a] Both for initial treatment and continuing treatment
[b] Dispensed prices calculated using the Efficient Funding of Chemotherapy (EFC) fees as in May 2018.
[c] Prices related to proposed special price arrangement which was presented in the revised minor submission lodged on 2 May 2018.

Treatment phase: Grandfathering

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Stage IV (metastatic) previously untreated
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) previously untreated non-small cell lung cancer
Treatment phase:	Grandfathering
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency

	☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have stable or responding disease, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to (date of listing), AND Patient must have a WHO performance status of 0 or 1, AND The treatment must not exceed a total of 7 doses at a maximum dose of 200 mg every 3 weeks for this condition under this restriction.
Population criteria:	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.
Administrative Advice	No increase in the maximum number of repeats will be authorised. In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. Special Pricing Arrangements apply.

Treatment phase: Continuing treatment

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Stage IV previously untreated
Condition:	Non-small cell lung cancer
PBS Indication:	Stage IV (metastatic) previously untreated non-small cell lung cancer
Treatment phase:	Continuing
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have stable or responding disease, AND The treatment must be the sole PBS-subsidised treatment for this condition, AND Patient must have previously been issued with an authority prescription for this drug for this indication,

	AND The treatment must not exceed a dose of 200 mg every 3 weeks, AND Treatment must not exceed 35 administrations or 2 years of ~~continuous treatment~~ *combined PBS-subsidised and non-PBS-subsidised therapy*.
Administrative Advice	No increase in the maximum number of repeats will be authorised. Special pricing arrangements apply

3 Background

Registration Status

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

3.2 Other TGA-approved indications include:

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

3.3 This is the fourth submission to the PBAC for pembrolizumab for the first-line treatment of NSCLC in patients whose tumours express PD-L1 at TPS ≥50%. The first two PBAC submissions were part of integrated codependent submissions considered in March and November 2017. The third was a streamlined minor resubmission to the PBAC in March 2018.

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

3.5 At the March 2017 PBAC meeting, an integrated codependent submission to list pembrolizumab as first-line treatment for patients with Stage IIIB/IV, PD-L1 TPS

≥50% NSCLC was rejected by the PBAC on the basis of unfavourable and uncertain cost-effectiveness. The PBAC also advised that there was uncertainty in selecting a PD-L1 expression threshold to define an optimal patient population mostly likely to respond to treatment (Paragraph 6.23, pembrolizumab 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 ≥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 would be 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 was 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 the PD-L1 test, 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 PSD).

3.7 The minor resubmission considered by the PBAC in March 2018 stated that MSAC endorsed the use of PD-L1 testing for eligibility to pembrolizumab and that its final ratification is expected following a positive PBAC recommendation.

Relevant previous PBAC consideration of nivolumab for NSCLC

3.8 The PBAC considered nivolumab for the treatment of NSCLC at the March 2016, November 2016 and March 2017 PBAC meetings.

3.9 At the March 2017 PBAC meeting, the PBAC recommended the Authority Required (Streamlined) listing of nivolumab for the treatment of locally advanced or metastatic, squamous or non-squamous NSCLC in patients who have progressed on or after prior platinum-based chemotherapy. As part of this consideration, the PBAC recommended inclusion of a rebate relating to patients over the age of 75 years, payable if the number of patients over 75 years initiating treatment exceeded a certain proportion of total initiators. In addition to the RSA for patient age, an RSA providing an overall cap on patient numbers and a dose-adjusted cost per patient with 100% rebate for utilisation over the caps would be required to address the concerns about use outside the restriction and uncertainty around treatment duration (paragraphs 6.48, 6.52, 7.6 and 7.7, nivolumab PSD, March 2017 PBAC meeting).

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 previous 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 PBAC 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 as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from individuals (10), health care professionals (8), and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with pembrolizumab, including improved quantity and quality of life without the significant side effects of chemotherapy. Many of the comments referred to the prohibitive cost of unsubsidised pembrolizumab.

5.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for this submission, on the basis of increased progression free survival and overall survival 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) as 5 out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement[1,2], based on a comparison with platinum-based chemotherapy.

Economic analysis

5.4 In the November 2017 major resubmission, a cost-effectiveness analysis and a cost-utility analysis were 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%).

5.5 The minor resubmission considered by the PBAC in March 2018 did not alter the economic model structure from March/November 2017, however it presented a respecified model. The current minor resubmission has again presented a respecified

[1] Reck M, Rodríguez-Abreu D, Robinson AG, et al: Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. New England Journal of Medicine 375:1823-1833, 2016

[2] Brahmer JR, Rodríguez-Abreu D, Robinson AG, et al: PL04a.01: Health-Related Quality of Life for Pembrolizumab vs Chemotherapy in Advanced NSCLC with PD-L1 TPS>50%: Data from KEYNOTE-024. Journal of Thoracic Oncology 12:S8-S9

model. A comparison of the revised model and the previous model is presented below.

Table 1: Comparison of the elements of the economic model in the March 2018 minor resubmission and the July 2018 minor resubmission

Model variable	March 2018 minor resubmission		July 2018 minor resubmission
	Minor resubmission	PBAC comments[b]	
Duration of pembrolizumab therapy	Assuming the same as duration of PFS	PBAC accepted time to treatment cessation approach presented in the minor overview with a cost per patient of $[redacted] [paras 5.14 and 6.1]	Using data on time-on-treatment from Trial KN-024 as advised by the PBAC, with a cost per patient of $[redacted]
Basis of PFS extrapolation beyond the duration of follow-up in the trial	Exclusion of PFS data between Weeks 0 and 9 in developing extrapolation	The minor resubmission's exclusion of the first 9 weeks of KM data for PFS did not follow the previous PBAC advice [para 6.5]	Inclusion of PFS data from Week 0 to Week 9 in developing extrapolation
Selection of parametric distribution to extrapolate PFS and OS curves	Pembrolizumab: exponential distribution for both PFS and OS Doublet chemotherapy: exponential distribution for both PFS and OS	It was uncertain whether the most conservative parametric models were chosen for PFS and OS extrapolation [para 6.6]	Using the most conservative extrapolations Pembrolizumab: exponential distribution for both PFS and OS Doublet chemotherapy: Generalised Gamma distribution for PFS and Gompertz distribution for OS
Proposed pembrolizumab rebate	[redacted]% rebate from [redacted] of treatment	The PBAC noted that time point from which a rebate applies ([redacted]) 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 [redacted] of treatment [para 6.4]	[redacted]%[a] rebate from [redacted] of treatment (around [redacted]% patients remaining on pembrolizumab by [redacted])
Other differences	**March 2018 minor resubmission**		**July 2018 minor resubmission**
	Minor resubmission	**PBAC comments**	
Extrapolation time point for PFS	97 weeks for both treatment arms	None	103 weeks for pembrolizumab and 97 weeks for doublet chemotherapy
Extrapolation time point for OS	97 weeks for both treatment arms	None	109 weeks for both treatment arms

KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival

[a] This was the rebate proposed by the sponsor in the 2nd May document subsequent to the minor resubmission.

[b] Ratified minutes for the March 2018 pembrolizumab submission.

Source: Table compiled based on the March 2018 minor resubmission, March 2018 PBAC Minutes and current minor resubmission

5.6 Overall, the main economic issues raised by the PBAC at the March 2018 meeting were addressed in this minor resubmission. In addition, the resubmission revised the time point of extrapolation (see table above). The change in this variable, however, would have negligible impacts on the result (1% difference).

5.7 Verification of the stepped economic analyses included in the minor resubmission is presented below.

Table 2: Revised stepped economic analyses

Parameters	ICER (Cost/QALY)
Base case as presented in the March 2018 minor resubmission	**$** [redacted] ***Revised: $*** [redacted]
Changes in the current minor resubmission	
1. KM data from Weeks 0-9 included to determine the PFS extrapolation (and changing the time point from which extrapolated data were used)	$ [redacted] *Revised:* [redacted][a]
2. 1 + Most conservation extrapolations	$ [redacted] *Revised: $* [redacted][a]
3. 2 + Use time-on treatment KM curves to estimate the treatment cost for pembrolizumab and chemotherapy	$ [redacted] *Revised: $* [redacted][a]
4. 3 + change of rebate to [redacted]% from [redacted] of treatment[b]	$ [redacted]

ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; PFS = progression-free survival; QALY = quality-adjusted life year

[a] In the March 2018 minor resubmission, the economic model erroneously applied a [redacted]% rebate from [redacted], not from [redacted] as proposed by the previous minor resubmission and as used in the financial analysis. The ICERs in italics were recalculated using the time point ([redacted]) for the rebate proposed in the previous minor resubmission.

[b] This was the rebate proposed by the sponsor in the 2nd May document subsequent to the minor resubmission.

Source: Table 3 of the minor resubmission and Table 1 of the 2nd May document subsequent to the minor resubmission.

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

Drug cost/patient/course: $[redacted]

5.8 The drug cost was estimated to be $[redacted] per patient per pembrolizumab course, based on the observed time-on-treatment from the KN-024 trial ([redacted] administrations) and a cost of $[redacted] per infusion, with a [redacted]% rebate applied on administrations from [redacted] onwards. The rebate proposed in the current resubmission results in a slightly reduced drug cost per treatment course, compared with $[redacted], which was calculated using the rebate proposed in the previous minor resubmission ([redacted]% rebate from [redacted] of treatment), and was accepted by the PBAC in March 2018 (paragraphs 5.14 and 6.1, pembrolizumab March 2018 PBAC PSD).

Estimated PBS usage & financial implications

<u>PBAC's previous consideration on the number of patients likely to receive pembrolizumab</u>

5.9 At the November 2017 meeting, the PBAC considered that substantial cost offsets from second-line nivolumab resulting from a PBS listing of first-line pembrolizumab in NSCLC would affect the RSA in the Deed of Agreement for nivolumab in NSCLC. The PBAC considered that, if pembrolizumab were 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 the proposed PBS listing of pembrolizumab would reduce the PBS expenditure on nivolumab, reducing the effect of its RSA, without necessarily

providing similar RSA across both immunotherapies (paragraph 7.16, pembrolizumab November 2017 PBAC PSD).

5.10 The minor resubmission considered by the PBAC in March 2018 maintained the same estimate of patient numbers as the November 2017 major resubmission. It also, 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 number of patients who would uptake pembrolizumab as a result of changing from first-line chemotherapy, and estimates on the number of patients who would uptake pembrolizumab but would not have received first-line chemotherapy.

5.11 The minor resubmission considered by the PBAC in March 2018 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
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.
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.
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].
Prevalence of PD-L1 TPS ≥ 50%	28.5%	Data on cohort of Australian patients from the KN-024 study.
2L nivolumab market replaced by 1L pembrolizumab	**19.53%**	Calculation = 78.6% x ((77.6% x 83.5%) + 22.4%) x 28.5%

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death ligand 1; TPS = tumour proportion score
Source: Table 3, pembrolizumab March 2018 PBAC Minutes

5.12 The March 2018 minor resubmission estimated neither the number of patients who currently receive nivolumab second-line, nor 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 grandfathered patients who would have otherwise received first-line chemotherapy.

5.13 At the March 2018 meeting, 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 were 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 disagreed with the minor resubmission's estimate of the large number of patients who would be eligible for pembrolizumab but would not subsequently have been eligible for nivolumab. 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 ( ) for an overall population which is about double Australia's population (paragraph 6.10, pembrolizumab March 2018 PBAC PSD).

Number of patients likely to receive pembrolizumab estimated by the current minor resubmission

5.14 The current minor resubmission took a similar approach to estimation of the extent of utilisation to the March 2018 minor resubmission. The main differences in the financial analyses between the two submissions are summarised in Table 4.

Table 4: Key differences between the financial inputs/assumptions in the March 2018 and July 2018 minor resubmissions

Variables/Assumptions	March 2018 minor resubmission	Current minor resubmission
Treatment rate of pembrolizumab	83.5% in Year 1, increasing to 84% in Year 2 and 85% in Years 3-6 (resubmission's estimate)	% (resubmission's estimate) for each listing year
Treatment rate of platinum-based doublet chemotherapy	60% (sponsor-commissioned ONCOSight report)	% (data from the Victorian Lung Cancer Registry data) for each listing year
Proportion of patients receiving 1L chemotherapy who would receive 2L nivolumab	64.2% (the KN-024 trial)	% (resubmission's estimate)
Number of candidates for grandfathering	(resubmission's estimate)	(resubmission's estimate)

Source: March 2018 pembrolizumab resubmission and current minor resubmission

5.15 The revised treatment rate for pembrolizumab assumed in the current minor resubmission (%), although lower than the previous resubmission's estimate (83.5%-85%), was much higher than the treatment rate of approximately 65% that the PBAC previously advised would be more reasonable for pembrolizumab (Paragraphs 5.26 and 6.8, pembrolizumab March 2018 PBAC PSD). In addition, the current resubmission's estimate of the incremental treatment rate of pembrolizumab versus chemotherapy (% = % – %) was higher than the 5% difference implied in the March 2018 PBAC PSD: the PBAC advised a treatment uptake rate of 65% for pembrolizumab versus 60% for chemotherapy (Paragraphs 5.26 and 6.8, pembrolizumab March 2018 PBAC PSD). Overall, the number of

patients likely to receive pembrolizumab and the number of patients who would otherwise receive chemotherapy followed by nivolumab are likely to have been overestimated by the current minor resubmission. Also, the market size for first-line treatment increased due to the listing of pembrolizumab has been overestimated compared to those that would be estimated using the previous PBAC advice.

5.16 The resubmission assumed [redacted]%, compared with 64.2% in the previous resubmission, as the treatment rate with second-line nivolumab for patients initiating on chemotherapy. However, this would not change the total number of pembrolizumab patients proposed by the minor resubmission (the estimate is only relevant to the treatment rate for first-line pembrolizumab, see Table 5 below), but would change the distribution of patients with nivolumab offset applied and new first-line pembrolizumab within the overall pembrolizumab population.

5.17 Refer to the "Comparison with related basis for agreed patient numbers for nivolumab in NSCLC" section below for further discussion regarding the treatment rates assumed in the current minor resubmission.

5.18 The resubmission's estimated numbers of patients likely to receive pembrolizumab if it gets listed are presented in Table 5.

Table 5: Estimates of numbers and types of NSCLC patients treated with pembrolizumab as presented in the current minor resubmission

	Population assumptions		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Patients who switch from chemotherapy to pembrolizumab Revised		[redacted][a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B	Incremental pembrolizumab patients (would not have had chemotherapy) Revised		[redacted][a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C1	Grandfathered patients	Patients who switched from chemotherapy to pembrolizumab Revised	[redacted][a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C2		Patients who have taken pembrolizumab but would not have received chemotherapy Revised	[redacted][a]					
	Total pembrolizumab patients (A + B + C)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D	Patients in whom cost offset of nivolumab was applied (75% x (A + C1))		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
E	Patients who would not have received second-line immunotherapy after progression with first-line chemotherapy (A – D)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F	New first-line pembrolizumab population (B + E) Revised		[redacted][a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total pembrolizumab patients (D + F)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Calculated during the evaluation, using the epidemiological data presented on the 'Epidemiology and Patient Number' spreadsheet in the "1L NSCLC Section 4_Budget Impact Model_PBAC Minor Resubmission_26 APRIL 2018.xlsx" workbook. (note that the wrong figures presented in this spreadsheet were not used to determine the financial implications associated with pembrolizumab listing)

[redacted]

Source: 'Patient Number Calculations' spreadsheet in the "1L NSCLC Section 4_Budget Impact Model_PBAC Minor Resubmission_26 APRIL 2018.xlsx" workbook

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year.

5.19 In comparison with the March 2018 resubmission, the current minor resubmission assumed: i) more patients switching from chemotherapy to pembrolizumab; ii) fewer incremental pembrolizumab patients; iii) fewer grandfathered patients; iv) more patients for whom cost offset of nivolumab would apply; v) fewer patients who would not have received second-line nivolumab; and vi) fewer new first-line pembrolizumab patients. The overall number of patients likely to receive pembrolizumab was slightly reduced by 3%-8% from the previous resubmission's estimate (Table 6).

Table 6: Comparison of numbers and types of NSCLC patients treated with pembrolizumab estimated in the current minor resubmission with the previous resubmission

	Population assumptions		Current resubmission	March 2018 resubmission	% change from previous submission
A	Patients who switch from chemotherapy to pembrolizumab		[redacted] in Year 1 to [redacted] in Year 6	[redacted] in Year 1 to [redacted] in Year 6	18% increase[a]
B	Incremental pembrolizumab patients (would not have had chemotherapy)		[redacted] in Year 1 to [redacted] in Year 6	[redacted] in Year 1 to [redacted] in Year 6	57%-60% reduction[b]
C1	Grandfathered patients	Patients who switched from chemotherapy to pembrolizumab	[redacted] in Year 1	[redacted] in Year 1	31% reduction[c]
C2		Patients who have taken pembrolizumab but would not have received chemotherapy	[redacted] in year 1	[redacted] in Year 3	
	Total pembrolizumab patients		[redacted] in Year 1 to [redacted] in Year 6	[redacted] in Year 1 to [redacted] in Year 6	3%-8% reduction[d]
D	Patients in whom cost offset of nivolumab was applied		[redacted] in Year 1 to [redacted] in Year 6	[redacted] in Year 1 to [redacted] in Year 6	31%-38% increase[e]
E	Patients who would not have received second-line immunotherapy after progression with first-line chemotherapy		[redacted] in Year 1 to [redacted] in Year 6	[redacted] in Year 1 to [redacted] in Year 6	17%-21% reduction[f]
F	New first-line pembrolizumab population		[redacted] in Year 1 to 527 in Year 6	[redacted] in Year 1 to [redacted] in Year 6	38%-40% reduction[g]
	Total pembrolizumab patients		[redacted] in Year 1 to [redacted] in Year 6	[redacted] in Year 1 to [redacted] in Year 6	3%-8% reduction[d]

[a] Due to the higher treatment rate for first-line doublet chemotherapy assumed in the current minor resubmission ([redacted]% vs 60% in the previous resubmission)

[b] Due to the assumed lower incremental treatment rate for pembrolizumab versus chemotherapy ([redacted]% vs 23.5%-25%)

[c] Primarily due to the lower number of grandfathering patients estimated in the current minor resubmission

[d] Due to the assumed lower treatment rate for first-line pembrolizumab ([redacted]% vs 83.5%-85%)

[e] Primarily due to the higher treatment rate for first-line chemotherapy ([redacted]% vs 60%) and higher proportion of patients receiving chemotherapy who would be treated with later-line nivolumab after disease progression (75% vs 64.2%) assumed in the current resubmission

[f] Primarily due to the higher treatment rate for first-line chemotherapy ([redacted]% vs 60%) but lower proportion of patients receiving chemotherapy who would not be treated with later-line nivolumab after disease progression (25% vs [redacted]%) assumed in the current resubmission

[g] Row F = Row B + Row E, refers to corresponding table notes 'b' and 'f' above

Source: Table compiled during the evaluation, based on Table 5 of this document and Table 4 of March 2018 PBAC Minutes

5.20 The PBAC's concern that the estimates of the numbers of patients in Australia were overestimated relative to the corresponding estimates from England with a larger population (paragraph 6.10, pembrolizumab March 2018 PBAC PSD) was not addressed in the current minor resubmission. This omission is important, because the publicly available estimates for England accord more closely with PBAC expectations when adjusted for overall population differences, and support the overall impression that the minor resubmission still overestimates the numbers of patients who would be eligible for pembrolizumab if listed as requested.

5.21 For further discussion, see the "Comparison with related basis for agreed patient numbers for nivolumab in NSCLC" section below.

Particular issues with number of grandfathered patients

5.22 The pre-PBAC response to the March 2018 resubmission stated that the sponsor had launched an early access program (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. A total of 46 patients were enrolled in the first 3 weeks of the EAP.

5.23 The calculation of the number of grandfathered patients is presented in Table 7. The current resubmission indicated that the number of grandfathering patients has been revised on the basis of the updated scope and timing of the EAP. However, the resubmission did not provide any further details regarding the estimation/revision of the number of candidates for grandfathering, i.e. prior to PD-L1 status consideration or eligibility for targeted therapies (Row A in Table 7).

Table 7: Calculation of the number of grandfathered patients in the current minor resubmission

A	Patients available for grandfathering	[redacted]
B	Number of patients that are PD-L1 positive (28.5% × A)	[redacted]
C	PD-L1+ non-squamous (77.6% × B)	[redacted]
D	PD-L1+ non-squamous, EGFR- and ALK- (83.5% × C)	[redacted]
E	PD-L1+ squamous (22.4% × A)	[redacted]
F	Patients that would have received chemotherapy ([redacted]% × (D + E))	[redacted]
G	Patients that would uptake pembrolizumab ([redacted]% × (D + E))	[redacted]
H	Patients who would uptake pembrolizumab, who would not uptake chemotherapy (G - F)	[redacted]

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; PD-L1 = programmed cell death ligand 1
Source: Figures calculated during the evaluation, using the epidemiological data presented on the 'Epidemiology and Patient Number' spreadsheet in the "1L NSCLC Section 4_Budget Impact Model_PBAC Minor Resubmission_26 APRIL 2018.xlsx" workbook

5.24 Compared to the March 2018 submission, the current minor resubmission assumed there would be lower numbers of grandfathered patients who would switch from chemotherapy to pembrolizumab ([redacted] vs [redacted] in the March 2018 resubmission, i.e. 16% reduction) and of grandfathered patients who would be treated with pembrolizumab but not uptake chemotherapy ([redacted] vs [redacted] in the March 2018 resubmission, i.e. 70% reduction).

5.25 At its March 2018 meeting, the PBAC noted that the inclusion of grandfathered patients from the prevalent pool in its epidemiological approach to estimate the size of the PBS population would affect any proposal to use a RSA to generate an upper cost per patient for pembrolizumab in order to achieve acceptable cost-effectiveness (paragraphs 5.29 and 6.9, pembrolizumab March 2018 PBAC PSD).

Comparison with related basis for agreed patient numbers for nivolumab in NSCLC

5.26 Both pembrolizumab and nivolumab are PD-1 inhibitors, with similar adverse event profiles, for treatment of NSCLC of all histological subtypes in patients with performance status of 0 or 1. As for the pembrolizumab submissions, the nivolumab submissions used an incidence-based approach to determine the nivolumab utilisation estimates. [redacted]

5.27 Table 8 compares the approach taken by this minor resubmission to the estimation of the numbers of patients who would have the cost of second-line nivolumab offset with the accepted nivolumab approach. The following are key differences between the two approaches:

- line of therapy: pembrolizumab first-line versus nivolumab second-line or third-line;
- disease stage: pembrolizumab for metastatic (Stage IV) disease versus nivolumab for locally advanced or metastatic (Stage IIIB/IV) disease; and
- NSCLC biomarker status: pembrolizumab for PD-L1 TPS ≥50%, EGFR- and ALK- versus nivolumab for NSCLC, regardless of PD-L1 expression or mutation status.

Table 8: Comparison of the agreed nivolumab approach and the resubmission's approach – nivolumab offset

	Agreed nivolumab approach	Current resubmission's approach
Source of data on incident NSCLC population	[redacted]	Sponsor-commissioned ONCOSight report
Number of patients with incident NSCLC	[redacted] in Year 2018 (Year 2 of listing), increasing to [redacted] in Year 2022 (Year 6 of listing)	[redacted] in Year 2018 (Year 1 of listing), increasing to [redacted] in Year 2022 (Year 5 of listing) [redacted]
Assumptions used to estimate number of patients receiving platinum-based doublet chemotherapy		
Non-squamous vs squamous NSCLC	[redacted]% vs [redacted]%	77.6% vs 22.4%
Distribution of disease stage	[redacted]	65% with Stage IIIB/IV, of which [redacted]% Stage IV[a]
Proportion of patients with PS 0 or 1	[redacted]	[redacted]%
Mutation status	[redacted]	EGFR- and ALK- in non-squamous NSCLC: 83.5%[b] PD-L1 TPS ≥ 50%: 28.5%
Treatment rate of platinum-based doublet chemotherapy	[redacted] • [redacted]% for squamous NSCLC • [redacted]% for non-squamous NSCLC	For Stage IV patients with PS of 0 or 1 who are PD-L1 TPS ≥50%, EGFR- and ALK-: [redacted]%

	Agreed nivolumab approach	Current resubmission's approach
Number of patients receiving platinum-based doublet chemotherapy in the respective target population	Non-squamous: [redacted] in Year 2018, increasing to [redacted] in Year 2022, Squamous: [redacted] in Year 2018, increasing to [redacted] in Year 2022	[redacted][c] in Year 2018, increasing to [redacted] in Year 2022
Number of patients receiving doublet chemotherapy for Stage IIIB/IV NSCLC, regardless of NSCLC mutation status	[redacted] in Year 2018, increasing to [redacted] in Year 2022	[redacted] in Year 2018, increasing to [redacted] in Year 2022[d] [redacted] than the estimate from the agreed nivolumab approach
Proportion of patients receiving doublet chemotherapy who would be treated with later-line nivolumab	Non-squamous: [redacted] Squamous: [redacted]% Overall: [redacted]%	[redacted]%

	Agreed nivolumab approach	Current resubmission's approach
Number of patients receiving later-line nivolumab in the respective target population	Non-squamous: [redacted] in Year 2018, increasing to [redacted] in Year 2022 Squamous: [redacted] in Year 2018, increasing to [redacted] in Year 2022	[redacted][c] in Year 2018, increasing to [redacted] in Year 2022
Number of patients receiving nivolumab for Stage IIIB/IV NSCLC, regardless of NSCLC biomarker status	**[redacted] in Year 2018, increasing to [redacted] in Year 2022[e]**	**[redacted] in Year 2018, increasing to [redacted] in Year 2022[f] [redacted] than the estimate from the agreed nivolumab approach**

[redacted]; ALK = anaplastic lymphoma kinase; DUSC = Drug Utilisation Sub-Committee; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death ligand-1; PS = performance status; TPS = tumour proportion score

[a] Number of patients progress from earlier stage to IV sourced from the sensitivity analysis presented in the DUSC advice (March 2017)

[b] 83.5% = 1 - 12.5% (EGFR+) - 4% (ALK+)

[c] Without taking into account grandfathered patients

[d] = number of patients receiving platinum-based doublet chemotherapy in Stage IV NSCLC with PD-L1 TPS ≥50%, EGFR- and ALK- ÷ 19.53% (see Table 3)

[e] [redacted]

[f] = number of patients receiving nivolumab in Stage IV NSCLC with PD-L1 TPS ≥50%, EGFR- and ALK- ÷ 19.53% (see Table 3)

Source: Table compiled based on the current pembrolizumab minor resubmission, nivolumab "PBS Non-squamous NSCLC vE 20170522.xlsx" workbook and nivolumab "PBS Squamous NSCLC vE 20170522.xlsx" workbook

5.28 The inputs/assumptions used in the approach proposed for pembrolizumab were not consistent with the approach previously accepted for nivolumab by the PBAC. The current pembrolizumab resubmission estimated the number of patients eligible for pembrolizumab, taking into account the eligibility criteria in terms of disease stage, NSCLC mutation status and performance status, and then applied a treatment rate to the resulting patient candidates. [redacted] The calculated proportion of NSCLC patients who would be treated with first-line doublet chemotherapy for Stage IIIB/IV NSCLC, regardless of NSCLC mutation status, was [redacted] in the pembrolizumab approach than in the nivolumab approach ([redacted]% vs [redacted]%[3]). This implies that the current pembrolizumab resubmission's estimate of the treatment rate for platinum-based doublet chemotherapy ([redacted]%) is an [redacted]. In addition, the uptake rate

[3] Calculated as the number of patients receiving doublet chemotherapy for Stage IIIB/IV NSCLC, regardless of NSCLC mutation status (Row 6 of Table 8) divided by the number of patients with incident NSCLC (Row 3 of Table 8)

of later-line nivolumab in patients receiving doublet chemotherapy was [redacted] in the current pembrolizumab submission than in the agreed nivolumab approach ([redacted]% vs [redacted]%). Overall, the differences between the two approaches have contributed to an [redacted] of the number of patients who would otherwise receive platinum-based chemotherapy and, more importantly, the number of patients for whom the sponsor is claiming a nivolumab cost offset.

5.29 Table 9 assesses the resubmission's estimates of two subpopulations of patients for pembrolizumab (i.e. (a) patients with nivolumab offset applied and (b) patients who would not have received second-line immunotherapy after progression (see Rows D and F of Table 5 above, repeated as Rows B and C of Table 9 below)) compared to the agreed nivolumab estimates in the Deed.

Table 9: Comparison of the agreed nivolumab approach and the resubmission's approach – nivolumab offset and new patients receiving first-line therapy

		Calendar years						
	Nivolumab Deed (as per estimates for the PBS listing starting 1 August 2017)	**1**	**2**	**3**	**4**	**5**	**6**	**7**
A	Total (squamous + non-squamous)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–
	Pembrolizumab (as per minor resubmission)	**–**	**1**	**2**	**3**	**4**	**5**	**6**
B	Patients in whom cost offset of nivolumab was applied[c]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C	New first-line pembrolizumab population[d]	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D	Total		[redacted][e]	[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[f]	–	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	Overall PD-1 inhibitor market (A + H)	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–

NSCLC = non-small cell lung cancer; PD-1 = programmed cell death 1

[a] Dose-adjusted estimates with grandfathering (Year 1 and Year 2 only) included

[b] Including [redacted] grandfathered patients in Year 1 and [redacted] grandfathered patients in Year 2 of listing as per estimates in the nivolumab Deed

[c] Row D of Table 5: [redacted]% x patients who switch from first-line chemotherapy to pembrolizumab (Row A ± Row C1) of Table 5)

[d] Row F of Table 5: 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

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

[f] See Table 3, the resubmission's estimate of the proportion of the second-line nivolumab market that would be replaced by pembrolizumab in the first-line setting

Source: Table compiled during the evaluation based on the nivolumab Deed and Table 5 of this document

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

5.30 The first subpopulation is those patients who would no longer receive second-line nivolumab if first-line pembrolizumab were to be listed. As pembrolizumab would be limited to those patients who are not EGFR or ALK+ 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). The actual percentages derived from the approach used in the minor resubmission to generate the financial estimates ([redacted]%-[redacted]%, Row F) are [redacted] than 19.53% which assumes all patients currently receiving nivolumab who are eligible for pembrolizumab would switch to pembrolizumab if it were to be listed. This is [redacted] and implies that the resubmission has [redacted] the number of patients for whom cost offset of nivolumab should apply, including by assuming a [redacted] uptake rate for doublet chemotherapy ([redacted]%) and a [redacted] treatment rate of subsequent nivolumab in patients receiving chemotherapy ([redacted]%). If these figures are applied to the [redacted] numbers of patients with Stage IIIB/IV NSCLC estimated to be taking nivolumab in the "current resubmission's approach" column of Table 8, the resulting percentages also [redacted] 19.53[redacted] suggesting that there may be multiple drivers of the [redacted] of patients receiving pembrolizumab as requested. In conclusion, comparing Row F with 19.53% provides a basis to reject the [redacted] of the first subpopulation of patients who would no longer receive nivolumab if first-line pembrolizumab were to be listed as presented in Row B.

5.31 In relation to the second subpopulation, the PBAC previously expressed its view that, if pembrolizumab were to become 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 (paragraph 7.16, pembrolizumab November 2017 PBAC PSD). This minor resubmission's estimates (Row C or Row G, which presents the expansion as a percentage, Table 9) are not consistent with this advice.

5.32 To investigate this further, it is possible to estimate the total eligible population that the minor resubmission infers would not receive nivolumab (Row H) by dividing the minor resubmission's estimates in Row C by 19.53% (the limit of pembrolizumab eligibility to those patients who are Stage IV, EGFR- and ALK- and whose tumours strongly express PD-L1). Adding this estimate to the agreed numbers of nivolumab patients gives the derived estimate that the previously accepted overall PD-1 inhibitor market would need to [redacted] if pembrolizumab were listed without these limitations (Row I). As this market growth would have to comprise patients who would not otherwise receive doublet chemotherapy and the chemotherapy-treated patients who would not have received second-line nivolumab after disease progression (Rows B and F of Table 5, the [redacted] growth rate of the PD-1 inhibitor market suggests that the minor resubmission has [redacted] the number of patients eligible for pembrolizumab compared to the corresponding accepted estimates for nivolumab. In particular, Row I of Table 9 indicates [redacted] estimates than either the corresponding Row A of Table 9 or the numbers of patients with Stage IIIB/IV NSCLC estimated to be taking nivolumab in

the "current resubmission's approach" column of Table 8. The causes of these [redacted] are not completely clear, but include the minor resubmission's estimates of the incremental first-line treatment rate due to the listing for pembrolizumab ([redacted]% = [redacted]% – [redacted]%) and the treatment rate for first-line platinum-based doublet chemotherapy in the absence of pembrolizumab ([redacted]%). In conclusion, comparing Row I with Row A provides a basis to reject the estimates of the second subpopulation of patients who would not have received second-line immunotherapy after progression if first-line pembrolizumab were to be listed as presented in Row C.

<u>Basis for estimating numbers of patients for pembrolizumab consistent with those agreed for nivolumab</u>

5.33 Given that the resubmission's approach [redacted] the extent of utilisation of pembrolizumab compared with the accepted nivolumab approach, an alternative basis for estimating the numbers of patients (and thus the financial implications) consistent with the PBAC's repeatedly stated preferred approach (pembrolizumab November 2017 PBAC PSD and March 2018 PBAC PSD) was developed. This approach starts with accepting numbers of patients each year from which nivolumab offsets would be expected (corresponding to Row D, Table 5) and then gives three options for the extra numbers of patients each year for which no nivolumab offset could be expected (corresponding to Row F, Table 5). These three options have been developed on relative increases of 5%, 10%, and 20%, with the PBAC to choose between the options based on the following:

1. 5% sourced from the March 2018 PBAC meeting which indicated that a 5% difference in uptake rates would be reasonable (pembrolizumab March 2018 PBAC PSD).
2. 10% based on the difference in uptake rates estimated in the current minor resubmission.
3. 20% based on the proportional use of second-line immunotherapy used for metastatic NSCLC in community practice settings, e.g. Nadler et al. (2018)[4].

5.34 This approach assumed a 100% nivolumab offset for patients who might be eligible for such an offset. As this results in an expected overestimate of the number of patients eligible for an offset (Row C of Table 10), it also results in an overestimation of the overall number of patients eligible for pembrolizumab using this alternative basis (Rows G to H of Table 10). Additional analyses were performed using a substitution rate of 75%. Results are presented in Table 11.

[4] Nadler, E., Espirito, J.L., Pavilack, M. et al. (2018) Treatment Patterns and Clinical Outcomes Among Metastatic Non-Small-Cell Lung Cancer Patients Treated in the Community Practice Setting. Clinical Lung Cancer, article in press. Accessed on 21 May 2018 at: https://reader.elsevier.com

Table 10: Estimated numbers of patients treated with pembrolizumab based on the agreed numbers of nivolumab patients (pembrolizumab substitution rate of 100%)

		Calendar years						
	Nivolumab Deed (as per estimates for the PBS listing starting 1 August 2017)	**1**	**2**	**3**	**4**	**5**	**6**	**7**
A	Total (squamous + non-squamous) [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–
	Pembrolizumab	**–**	**1**	**2**	**3**	**4**	**5**	**6**
B	Limiting the pembrolizumab population to Stage IV, PD-L1+, EGFR-, ALK- NSCLC		19.53%	19.53%	19.53%	19.53%	19.53%	19.53%
C	Pembrolizumab patients with nivolumab offset applied, assuming 100% substitution rate (A x B x 100%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	New pembrolizumab patients							
D	Additional 5% (C x 5%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
E	Additional 10% (C x 10%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F	Additional 20% (C x 20%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total pembrolizumab population							
G	Immunotherapy market growth of 5% due to the listing of pembrolizumab (C+D)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H	Immunotherapy market growth of 10% due to the listing of pembrolizumab (C+E)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
I	Immunotherapy market growth of 20% due to the listing of pembrolizumab (C+F)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

[a] Dose-adjusted estimates with grandfathering (Year 1 and Year 2 only) included

[b] Including [redacted] grandfathered patients in Year 1 and [redacted] grandfathered patients in Year 2 of listing as per estimates in the nivolumab Deed

[c] = 19.53% x the number of nivolumab patients in Year 7 of listing (n=[redacted], extrapolated by assuming a linear growth from Year 3 to Year 6)

Source: Table compiled during the evaluation

Table 11: Estimated numbers of patients treated with pembrolizumab based on the agreed numbers of nivolumab patients (pembrolizumab substitution rate of 75%)

		Calendar years						
	Nivolumab Deed (as per estimates for the PBS listing starting 1 August 2017)	**1**	**2**	**3**	**4**	**5**	**6**	**7**
A	Total (squamous + non-squamous)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–
	Pembrolizumab	**–**	**1**	**2**	**3**	**4**	**5**	**6**
B	Limiting the pembrolizumab population to Stage IV, PD-L1+, EGFR-, ALK- NSCLC		19.53%	19.53%	19.53%	19.53%	19.53%	19.53%
C	Nivolumab-treated patients with Stage IV, PD-L1+, EGFR-, ALK- NSCLC (A x B)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D	Pembrolizumab patients with nivolumab offset applied (C x 75%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	New pembrolizumab patients							
E	Additional 5% (C x 5%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F	Additional 10% (C x 10%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
G	Additional 20% (C x 20%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total pembrolizumab population							
H	Immunotherapy market growth of 5% due to the listing of pembrolizumab (D+E)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
I	Immunotherapy market growth of 10% due to the listing of pembrolizumab (D+F)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
J	Immunotherapy market growth of 20% due to the listing of pembrolizumab (D+G)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

[a] Dose-adjusted estimates with grandfathering (Year 1 and Year 2 only) included

[b] Including [redacted] grandfathered patients in Year 1 and [redacted] grandfathered patients in Year 2 of listing as per estimates in the nivolumab Deed

[c] = 19.53% x the number of nivolumab patients in Year 7 of listing (n=[redacted], extrapolated by assuming a linear growth from Year 3 to Year 6)

Source: Table compiled during the evaluation

5.35 The numbers of patients who would be treated with pembrolizumab calculated based on the nivolumab Deed are [redacted] than the resubmission's estimates if a growth rate of 20% is assumed for the immunotherapy market due to the listing of first-line pembrolizumab ([redacted] in Year 6, assuming a pembrolizumab substitution rate of 75%-100%, vs [redacted] in Year 6 estimated by the minor resubmission).

5.36 In its pre-PBAC response, the sponsor provided details of enrolments in its pembrolizumab Product Familiarisation Program (PFP) and presented a revised proposal for estimating the eligible population accounting for PFP enrolled patients. The sponsor considered that 100% of patients who would have taken nivolumab might be eligible to receive pembrolizumab. The sponsor argued that for a patient who is eligible for subsidised pembrolizumab as a first-line treatment, it would not make clinical sense to prescribe chemotherapy as a first-line treatment.

Financial implications based on revised estimates of numbers of patients

5.37 A comparison of the net costs to the PBS as a result of listing pembrolizumab estimated in the minor resubmission and the revised approach above is presented in the table below.

Table 12: Comparison of net cost to the PBS using different approaches

Net cost to PBS	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Minor resubmission[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
If 100% patients treated with nivolumab who are eligible for pembrolizumab will receive pembrolizumab if it gets listed						
Assuming an additional 5% new pembrolizumab patients[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assuming an additional 10% new pembrolizumab patients[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assuming an additional 20% new pembrolizumab patients[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
If 75% patients treated with nivolumab who are eligible for pembrolizumab will receive pembrolizumab if it gets listed						
Assuming an additional 5% new pembrolizumab patients[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assuming an additional 10% new pembrolizumab patients[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assuming an additional 20% new pembrolizumab patients[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Using the rebate proposed by the sponsor in the 2nd May document subsequent to the minor resubmission ([redacted]% rebate from [redacted] onwards).
[b] A patient co-payment was erroneously assumed for each comparator medicine administration, rather than per original prescription. This was corrected during the evaluation.
[c] Assuming 100% of patients receiving pembrolizumab would otherwise receive platinum-based doublet chemotherapy. Although this proportion remains uncertain, it would only have a minimal impact on the net cost to the PBS, given the low cost for chemotherapy relative to the immunotherapy (pembrolizumab or nivolumab) cost
Source: Table compiled during the evaluation

The redacted table shows that at Year 6, the estimated net cost to the PBS would be $30 - $60 million.

5.38 The minor resubmission estimated a net cost to the PBS of $30 – $60 million in Year 6 of listing, increasing to $60 - $100 million per year in Year 6 of listing. The extent of cost offset per patient is the product of the price of nivolumab multiplied by the duration of therapy of nivolumab. The full details could not be provided to the sponsor of pembrolizumab unless (and not before) the PBAC recommended listing pembrolizumab in NSCLC.

5.39 Assuming that the number of PBS target patients being treated with immunotherapy would increase by 5%, 10% or 20% as a result of the availability of first-line pembrolizumab and that 75%-100% patients currently receiving nivolumab who are eligible for pembrolizumab would switch to first-line pembrolizumab, the net cost to the PBS over the first 6 years of listing would [redacted] from the

submission's estimate, primarily due to the estimated [redacted] eligible population likely to be treated.

Risk Sharing Arrangement

5.40 The minor resubmission proposed both a special pricing arrangement and a RSA ([redacted]% rebate on subsequent pembrolizumab costs for those patients who are treated with pembrolizumab for [redacted] or more).

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

6 PBAC outcome

6.1 The PBAC recommended the listing of pembrolizumab under special arrangements under Section 100 (Efficient funding of chemotherapy) as an Authority Required (STREAMLINED) item for the first-line treatment of metastatic NSCLC in patients whose tumours express PD-L1 at TPS ≥50%, on the basis of acceptable incremental cost-effectiveness within an acceptable overall net cost to the PBS each year of eligible patients defined by this listing.

6.2 The PBAC recalled that it had previously considered that the sponsor's claims of superior comparative effectiveness (in terms of both progression-free survival and overall survival) and superior comparative safety, relative to platinum-based doublet chemotherapy, were both reasonable and that the trial data presented were robust (Paragraph 7.6, pembrolizumab Public Summary Document, November 2017).

6.3 The PBAC considered that this minor resubmission had adequately addressed the Committee's outstanding concerns from the March 2018 submission in relation to the economic evaluation. The PBAC recalled that, in its consideration of the March 2018 submission, it had accepted a respecified basis of the economic model which estimated a drug cost per treatment course with pembrolizumab of $[redacted] directly from the extrapolated time to treatment cessation from the KN-024 trial with a resulting revised ICER of $45,000/QALY – $75,000/QALY (paragraphs 5.14 and 6.1, pembrolizumab March 2018 PBAC minutes). The PBAC noted that the pembrolizumab drug cost for this resubmission was estimated to be slightly less than the March 2018 submission ($[redacted] per patient per pembrolizumab course) based on the observed time-on-treatment from the KN-024 trial ([redacted] administrations) and a cost of $[redacted] per infusion, with a [redacted]% rebate applied on administrations from [redacted] onwards.

6.4 The PBAC considered that the sponsor's estimates regarding the eligible patient population were overestimated. The PBAC reiterated its previous consideration that there would only be a minor increase in the number of patients treated for metastatic Stage IV NSCLC beyond what was accepted for the subsidisation cap for nivolumab (Paragraph 5.35, pembrolizumab PSD, March 2018). The PBAC noted the possible explanations given in Section 5 for why the sponsor's estimates could not be relied upon. During the evaluation process, an additional method of estimating the

patient population was developed. This approach was instead considered acceptable by the PBAC, and formed the basis for the Committee's recommendation.

6.5 The PBAC considered the sponsor's assertion that 100% of patients who would otherwise have been treated with nivolumab would receive pembrolizumab if they were eligible was reasonable. The PBAC noted that it was unlikely that clinicians would prescribe chemotherapy as a first-line treatment, followed by a PD-1 inhibitor (nivolumab) as a second-line treatment, if a PD-1 inhibitor (pembrolizumab) were available as a first-line therapy.

6.6 The PBAC reiterated its March 2018 view that the extra numbers of patients each year for which no nivolumab offset could be expected should be limited to an extra 5% beyond the estimated numbers of patients each year for whom nivolumab cost offsets are expected. This 5% increase each year primarily accounts for those patients who would not have been considered eligible for nivolumab because they would not have been considered eligible for first-line chemotherapy.

6.7 The PBAC therefore accepted the revised financial estimates developed during the evaluation based on the following main parameters:

a. 19.53 percent of nivolumab use in second-line treatment of locally advanced or metastatic NSCLC each year would be substituted by pembrolizumab use in first-line treatment of metastatic NSCLC in patients whose tumours express PD-L1 at TPS ≥50%

b. an extra 5 percent each year beyond the estimates for each year calculated by a. to account for those patients who would not have been considered eligible for nivolumab because they would not have been considered eligible for first-line chemotherapy

c. the inclusion, in the first year of listing, of the sponsor's estimate of the number of patients who would be grandfathered to pembrolizumab, noting that the majority of these patients would already be resulting in reduced use of second-line nivolumab.

The PBAC considered that the projected eligible population for pembrolizumab in the requested population was reasonable based on this approach: [redacted] patients in each calendar year.

6.8 The PBAC advised that a risk sharing arrangement should be established with the subsidisation cap based on the revised eligible number of patients with a 100% rebate beyond the subsidisation cap to mitigate the overall budgetary risk to Government, consistent with the current 100% rebate in the risk sharing arrangement for nivolumab that this pembrolizumab risk sharing arrangement would need to join. The PBAC noted that pembrolizumab's place in the therapeutic pathway for the treatment of NSCLC is still uncertain, as clinicians may prescribe pembrolizumab in combination with, not instead of, platinum-based doublet chemotherapy.

6.9 The PBAC considered that a future review of the NSCLC immunotherapy market immunotherapy market by the Drug Utilisation Sub-Committee was warranted.

6.10 The PBAC advised that both the proposed restriction of pembrolizumab as a first-line therapy for metastatic NSCLC and the restriction of nivolumab as a second-line therapy for the same indication include sufficient provisions to ensure that the PBS does not subsidise sequential immunotherapy for NSCLC.

6.11 The PBAC advised that the Early Supply Rule should not apply to this listing of pembrolizumab.

6.12 The PBAC advised that, under subsection 101(3BA) of the *National Health Act 1953*, pembrolizumab should not be treated as interchangeable on an individual patient basis with any other drugs.

6.13 The PBAC advised that pembrolizumab is not suitable for prescribing by nurse practitioners.

6.14 The PBAC noted that this submission is not eligible for an Independent Review as it has received a positive recommendation.

Outcome:
Recommended

7 Recommended Listing

Add new items: Restriction to be finalised

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Proprietary Name and Manufacturer	
PEMBROLIZUMAB 50 mg injection: powder for, 1 vial [a] 100 mg/4 mL injection, 1 vial [a]	200 mg	6 [a]	Keytruda®	Merck Sharp & Dohme (AU) Pty Ltd

Treatment phase: Initial treatment

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Stage IV (metastatic) previously untreated
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) previously untreated non-small cell lung cancer
Treatment phase:	Initial
Restriction Level / Method:	☒Streamlined
Clinical criteria:	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 7 doses at a maximum dose of 200 mg every 3 weeks for this condition under this restriction.
Population criteria:	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.
Administrative Advice	No increase in the maximum number of repeats will be authorised. In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. Special pricing arrangements apply.

[a] Both for initial treatment and continuing treatment

Treatment phase: Grandfathering

Category / Program	Section 100 – Efficient funding of chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Stage IV (metastatic) previously untreated
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IV (metastatic) previously untreated non-small cell lung cancer
Treatment phase:	Grandfathering
Restriction Level / Method:	☒Streamlined
Clinical criteria:	Patient must have stable or responding disease, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to (date of listing), AND Patient must have a WHO performance status of 0 or 1, AND The treatment must not exceed a total of 7 doses at a maximum dose of 200 mg every 3 weeks for this condition under this restriction.
Population criteria:	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.
Administrative Advice	No increase in the maximum number of repeats will be authorised. In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this

	should be confirmed through a confirmatory scan, taken at least 4 weeks later. Special Pricing Arrangements apply.

Treatment phase: Continuing treatment

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

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.