6.03 PEMBROLIZUMAB

Solution concentrate for I.V. infusion 100 mg in 4 mL, Keytruda®, Merck Sharp and Dohme (Australia) Pty Ltd.

1 Purpose of submission

1.1 The submission requested expansion of the existing PBS listing for pembrolizumab for the unresectable Stage III or Stage IV malignant melanoma, to allow first-line therapy in patients who are positive for a BRAF V600 mutation.

1.2 The submission also suggested changes to the current restrictions for BRAF±MEK inhibitors to allow their use as second-line therapy following progression on immunotherapy, enabling clinicians to determine the optimal treatment sequence.

1.3 The submission was based on a cost-minimisation analysis of pembrolizumab versus nivolumab. The submission assumed that nivolumab would be approved for first line treatment of the target population at the November 2019 PBAC meeting.

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

Component	Description
Population	Unresectable stage III or stage IV metastatic melanoma adult patients with a V600 BRAF mutation, who have not received prior treatment for this condition
Intervention	Pembrolizumab monotherapy: 200 mg IV Q3W or 400 mg IV Q6W[1]
Comparator	Nivolumab monotherapy: either 3 mg/kg Q2W, or 240 mg Q2W, or 480 mg Q4W
Outcomes	OS, PFS, adverse events
Clinical claim	In previously untreated metastatic melanoma patients with a V600 BRAF mutation, pembrolizumab is as effective as nivolumab in terms of efficacy outcomes and has a similar safety profile to nivolumab

IV = intravenous; OS = overall survival; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; Q6W = every 6 weeks.

[1] The 400 mg dose Q6W has been recommended by TGA (pp- 4, 64-65 of Keytruda Product Information) and is being considered by PBAC at the March 2020 meeting.

Source: Table 1.1-1, pp 9-10 of the submission, and compiled during the evaluation.

2 Background

Registration status

2.1 Relevant to the current submission, pembrolizumab was listed on the Australian Register of Therapeutic Goods on 16 April 2015 as monotherapy for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma, regardless of the BRAF mutation status.

Previous PBAC consideration

2.2 Pembrolizumab is currently listed on the PBS for unresectable Stage III or Stage IV malignant melanoma patients as:

- First line immunotherapy for the BRAF V600 mutation negative subpopulation.
- Later-line therapy for the BRAF mutation positive subpopulation after the failure of the first line treatment with a BRAF inhibitor (with or without a MEK inhibitor), unless contraindicated or not tolerated.

2.3 Pembrolizumab has not previously been considered by the PBAC for the target population within the submission.

2.4 At the November 2019 meeting the PBAC recommended nivolumab and nivolumab + ipilimumab as first-line immunotherapeutic agents for BRAF mutant unresectable malignant melanoma patients. The PBS restrictions for nivolumab and ipilimumab were extended to include this indication on 1 March 2020.

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

3 Requested listing

3.1 The submission proposed listing on a cost-minimisation basis, with the final effective price of pembrolizumab monotherapy to be determined based on the effective approved ex-manufacturer prices (AEMP) of nivolumab.

Essential elements of the requested listing for pembrolizumab

Name, Restriction, Manner of administration and form	Maximum Amount	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
PEMBROLIZUMAB 100 mg vial for IV infusion	200 mg	5	Published price[1] $8,559.06 (public) $8,717.46 (private) Effective price[2] To be determined	Keytruda® Merck Sharp and Dohme (Australia) Pty Ltd

Category/Program:	Section 100 - Efficient funding of Chemotherapy
Prescriber type	☒Medical Practitioners
PBS indication:	Unresectable stage III or stage IV metastatic malignant melanoma
Condition:	Malignant melanoma
Treatment phase:	Initial Treatment
Restriction:	☒ Streamlined
Clinical criteria:	The patient must not have received prior treatment with ipilimumab or a programmed cell death-1 (PD-1) inhibitor for this condition, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND The treatment must not exceed a total of 6 doses.
Prescriber Instructions:	In the first few months after the 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.
Administrative Advice:	No increase in the maximum quantity or number of units or number of repeats will be authorised. Patient must be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.

[1] The published prices were taken from the 1 December 2019 PBS update for the Efficient Funding of Chemotherapy Supplement.
[2] The submission proposed listing on a cost-minimisation basis against the effective price of nivolumab.
Source: Compiled during the evaluation based on Table 1.4-1 and Table 1.4-2, pp14-15 of the submission.

3.2 The restrictions for continuing treatment with pembrolizumab were unchanged from the current restrictions, and no grandfathering arrangements apply to this submission.

3.3 The current PBS listings for initial treatment with pembrolizumab are dependent on the patients' BRAF mutation status. The submission proposed to delete the initial treatment listings which restrict the use of pembrolizumab in patients with BRAF mutation positive melanomas to the second line setting after the failure of BRAF/MEK inhibitors. It also proposed modifying the current initial treatment listings for BRAF V600 mutation negative melanoma by removing the clinical criterion 'The condition must be negative for a BRAF V600 mutation'.

3.4 The requested amendments are consistent with the TGA indication for pembrolizumab for unresectable Stage III or Stage IV malignant melanoma, which does not restrict its use either by the line of therapy or BRAF mutation status.

3.5 The requested restriction was consistent with the eligibility criteria for the key pembrolizumab (KN006) and nivolumab (CM067) trials, both of which excluded patients who had received prior first line systemic therapy with ipilimumab, a programmed cell death-1 (PD-1) or a programmed cell death-ligand 1 (PD-L1) inhibitor.

3.6 The submission acknowledged the need for availability of BRAF±MEK inhibitor therapy after progression on the first line immunotherapy in the target population.

3.7 Current Australian and international guidelines[a] recommend the use of first line immunotherapy in asymptomatic patients with slow-growing tumours due to its ability to produce long term treatment-free survival. First line BRAF±MEK targeted therapy is recommended for more aggressive and highly symptomatic disease as it is associated with more short term rapid and reliable responses. The September 2019 update for European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for cutaneous melanoma reflected the recent changes which state that "despite the lack of direct randomised trials, recent meta-analyses show the BRAF±MEK targeted therapy to have better outcomes within the first 12 months of treatment whereas immunotherapy patients may have a better survival after one year" (Michielin, 2019).[b]

3.8 The submission noted that two head-to-head randomised controlled trials are currently underway to determine the optimal sequence and duration of therapy of

[a] Cancer Council of Australia. Summary of recommendations and practice points: Clinical practice guidelines for the diagnosis and management of melanoma, Practice points 6, 7. Source: https://wiki.cancer.org.au/australia/Guidelines:Immunotherapy_for_melanoma_recommendations
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Melanoma. Version 2.2019. Source: www.nccn.org/

[b] O Michielin, A van Akkooi, P Ascierto, R Dummer, U Keilholz, ESMO Guidelines Committee. (2019). Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. https://doi.org/10.1093/annonc/mdz411.

nivolumab + ipilimumab in the target population. The SECOMBIT[c] trial (NCT02631447) compares the combination therapy of nivolumab + ipilimumab with encorafenib + binimetinib (BRAF+MEK) inhibitors, whereas DREAMseq[d] (NCT02224781) compares the sequence and duration of BRAF±MEK inhibitor therapy followed by combination immunotherapy or combination immunotherapy followed by BRAF±MEK inhibitor therapy.

3.9 The consensus in various guidelines is that while the optimal treatment sequence is the subject of ongoing investigation, in practice, the treatment sequence should be based on clinician and patient preference.

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

4 Population and disease

4.1 Australia has one of the highest rates of melanoma in the world, with the age-standardised incidence rate of 52 cases per 100,000 people in Australia.[e] Melanoma was the fourth most commonly diagnosed cancer in Australia in 2015. The target population in the submission was unresectable Stage III or Stage IV systemic treatment naïve melanoma patients who are positive for a BRAF V600 mutation.

4.2 BRAF±MEK inhibitors are currently PBS listed for the target population, with nivolumab, as monotherapy or in combination with ipilimumab, recommended for the target population at the November 2019 PBAC meeting. As per the current Australian and international guidelines, the submission proposed pembrolizumab immunotherapy as an alternative treatment for the target population.

4.3 Pembrolizumab is a humanised monoclonal antibody which blocks the PD-1 receptor. PD-1 is an important immune checkpoint molecule that is expressed on the surface of activated T-cells. Many cancers, including melanoma, produce proteins (PD-L1 and PD-L2) that bind to PD-1, thus negating the ability of T-cells to kill cancer cells. Pembrolizumab prevents the binding of PD-L1 and PD-L2 to PD-1, allowing the immune system to target and destroy cancer cells.

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

[c] SECOMBIT has the following treatment arms: ENCO+BINI followed by NIVO+IPI; NIVO+IPI followed by ENCO+BINI; ENCO+BINI for 8 weeks, then NIVO+IPI until progression, followed by ENCO+BINI post-progression

[d] DREAMseq includes the following therapy sequence: NIVO on day 1 followed by IPI on day 22; NIVO on days 1,15,29; various BRAF inhibitors on days 1-42; NIVO days 1 and 22 followed by IPI days 1-22; NIVO days 1,15,29.

[e] Cancer Australia. Melanoma of the skin statistics. Last updated: 26/08/2019. Source: https://melanoma.canceraustralia.gov.au/statistics

5 Comparator

5.1 The submission nominated nivolumab monotherapy as the sole comparator under the assumption that it would receive a positive recommendation in the November 2019 PBAC meeting.

5.2 Given that nivolumab was recommended by the PBAC for the same indication in November 2019, the ESC considered that it was a relevant comparator. As BRAF±MEK inhibitor therapy is the current standard first line treatment option for the target population, it could also have been considered as a main comparator. The PBAC considered nivolumab was the appropriate comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from an organisation (1) via the Consumer Comments facility on the PBS website.

6.3 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the pembrolizumab submission, categorising it as one of the therapies of "high priority for PBS listing" on the basis of the KN006 trial. The PBAC noted that the MOGA was unable to present a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab as a first-line therapy in BRAF mutant patients with unresectable or metastatic melanoma, as there are no direct comparisons of pembrolizumab versus the current PBS-listed treatments (BRAF±MEK inhibitors) in this setting.

Clinical trials

6.4 The submission was based on two clinical trials:

- KN006 was an open-label, three-arm randomised controlled trial comparing two dose frequencies of pembrolizumab (10 mg/kg given every 2 weeks (N=278) and 10 mg/kg given every 3 weeks (N=277)) with ipilimumab monotherapy (N=278) in Stage III/IV unresectable malignant melanoma patients. This submission compared the relevant subgroup of systemic treatment naïve BRAF mutation positive unresectable malignant melanoma patients comprising of pembrolizumab (both dose frequencies combined (N=108)) and ipilimumab (N=55).
- CM067 was a randomised double-blind trial comparing nivolumab monotherapy (N=313) or nivolumab + ipilimumab combination therapy (N=313) with

ipilimumab monotherapy (N=311) in Stage III/IV unresectable malignant melanoma patients. This submission compared the relevant subgroup of systemic treatment naïve BRAF mutation positive unresectable malignant melanoma patients comprising of nivolumab alone (N=98) and ipilimumab (N=100).

6.5 Details of the trials are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication Citation
KN006	A Multicentre, Randomised Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of Pembrolizumab (MK-3475) Compared to Ipilimumab in Patients with Advanced Melanoma.	August 2015
	Robert C, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study.	Lancet Oncol. 2019 Sep;20(9):1239-1251
	Long GV, et al. 4-year survival and outcomes after cessation of pembrolizumab (pembro) after 2-years in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in KEYNOTE-006.	J of Clin Onc. 2018 May 2018
	Schachter J, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006).	Lancet. 2017 Oct 21;390(10105):1853-1862
CM067	Clinical Study Report - not publicly available	
	Larkin J, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma.	N Engl J Med. 2019 Sep 28
	Hodi FS, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Erratum in: Lancet Oncol. 2018 Dec;19(12):e668.	Lancet Oncol. 2018 Nov;19(11):1480-1492
	Larkin J, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma.	N Engl J Med. 2015 Jul 2;373(1):23-34
	Abstracts: Hodi FS, et al. LBA44. Overall survival at 4 years of follow-up in a phase III trial of nivolumab plus ipilimumab combination therapy in advanced melanoma (CheckMate 067).	Annals of Oncology, Volume 29, Issue suppl_8, October 2018
	Overall survival (OS) results from a phase III trial of nivolumab (NIVO) combined with ipilimumab (IPI) in treatment-naïve patients with advanced melanoma (CheckMate 067).	Cancer Res July 1 2017 (77) (13 Supplement) CT075

Source: Table 2.1-1, p22 of the submission.

6.6 Four network meta-analyses[f] identified during the evaluation compared the efficacy and safety of various therapeutic combinations for the target population. These

[f] Franken, M. G., et al. (2019). A systematic literature review and network meta-analysis of effectiveness and safety outcomes in advanced melanoma. European Journal of Cancer, 123, 58-71.

studies reported BRAF±MEK inhibitor therapy to be more efficacious in the first line setting while immunotherapies had a better safety profile. However, due to the lack of direct randomised controlled trial comparison and underlying heterogeneity, the conclusions presented from these meta-analyses are uncertain.

6.7 The key features of the randomised trials are summarised in Table 3. The submission was based on an indirect comparison between pembrolizumab and nivolumab, with ipilimumab as the common comparator.

6.8 The submission stated that the total population in CM067 was compared with the previously untreated BRAF mutation positive subgroup of KN006 to evaluate safety outcomes, whereas only BRAF mutant treatment naïve subgroups were compared for the efficacy outcomes of progression free survival (PFS) and overall survival (OS).

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Pembrolizumab vs. Ipilimumab						
KN006	PEMBRO: 108[a] IPI: 55[a]	R, OL, MC minimum 5 years[b]	Low[c]	BRAF mutant unresectable Stage III or Stage IV melanoma patients who have not been previously treated with BRAF±MEK or immunotherapy	OS, PFS	Used
Nivolumab vs. Ipilimumab						
CM067	NIVO: 98[a] IPI: 100[a]	R, DB, MC minimum 4 years[b]	Low	BRAF mutant unresectable Stage III or Stage IV melanoma patients who have not been previously treated with BRAF±MEK or immunotherapy	OS, PFS	Used

DB = double blind; IPI= ipilimumab; MC = multi-centre; NIVO= nivolumab; OL = open label; OS = overall survival; PEMBRO = pembrolizumab; PFS = progression-free survival; R = randomised.

[a] Number of patients in the first line BRAF mutation positive relevant subgroup.

[b] Minimum follow-up in all patients alive at the time of analysis.

[c] A high-risk of subjective bias for subjective outcomes was inherently present due to the open label design of the study. However, in KN006, the analysis and reporting team were blinded to the treatment assignments (p132, KN006 CSR).

Source: Table based on sections 2.3 and 2.4 of the submission.

6.9 Notable differences between the patients in the trials included the greater proportion with ECOG[g] level 1 and elevated lactate dehydrogenase[h] levels in CM067 compared with KN006, suggesting that patients in CM067 may have had more advanced disease.

Garzón-Orjuela, N., et al. (2019). Efficacy and safety of dabrafenib–trametinib in the treatment of unresectable advanced/metastatic melanoma with BRAF-V600 mutation: a systematic review and network meta-analysis. Dermatologic therapy.

An, Q., & Liu., Z. (2019). Comparative efficacy and safety of combination therapies for advanced melanoma: a network meta-analysis. BMC cancer, 19(1), 43.

Zoratti, M. J., et al. (2019). Network meta-analysis of therapies for previously untreated advanced BRAF-mutated melanoma. Cancer treatment reviews.

[g] Eastern Cooperative Oncology Group (ECOG) performance scores range from 0 to 5 with a score of 1 indicating the patient is symptomatic of disease, but completely mobile. A score of O indicates asymptomatic disease and 5 indicates death. Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649.

[h] Lactate dehydrogenase (LDH) levels are associated with increased resistance to therapy.

However, KN006 had a slightly greater proportion of patients with brain metastasis than CM067, as these patients were excluded from CM067 but not from KN006. Another key difference was that 9.3% of the BRAF mutant subgroup population in KN006 had received first line therapy (but not immunotherapy with PD-L1/PD-1 inhibitor or ipilimumab), whereas no CM067 participants received prior systemic treatment with BRAF±MEK inhibitors or PD-L1/PD-1/ipilimumab immunotherapy.

6.10 The submission claimed that differences in baseline patient characteristics between the two trials were unlikely to substantially impact the results of the indirect comparison. Although the patient characteristics of the two trials were broadly similar, a statistical population adjustment method, such as a Matching-Adjusted Indirect Comparison or Simulated Treatment Comparison, could have been utilised to address any lack of exchangeability of treatment effects between the two trials. The sponsor stated that such a technique was not utilised because baseline characteristics for the target population in trial CM067 were not available, and because any assumptions made on the makeup of the baseline characteristics for the BRAF mutant subpopulation would introduce more uncertainty and bias. The ESC considered that this explanation was reasonable.

6.11 The submission provided no information on subsequent treatments for CM067. A greater proportion of patients in KN006 received subsequent treatments in the ipilimumab control group (79%) compared to the two pembrolizumab arms (54%). The Pre-Sub-Committee Response (PSCR) stated that in the intention to treat population of CM067 the use of subsequent therapies (75% in the ipilimumab arm and 58% in the nivolumab arm) was similar to the BRAF mutant subgroup in the KN006. Data from the BRAF mutant subgroup in CM067 were not available.

6.12 Due to the lack of head-to-head randomised trials, the indirect comparisons made in the submission increased the overall risk of bias.

6.13 Differences were noted in the rates of discontinuation between the ipilimumab arm (36%) and the pembrolizumab arms (75% and 79%) of KN006 due to progressive disease, despite better PFS in the pembrolizumab arms. The PSCR stated that this was due to ipilimumab being administered for 12 weeks only; whereas, pembrolizumab is continued generally until progression or death.

6.14 For trial KN006, a 10 mg/kg dose of pembrolizumab was administered either every 2 weeks (Q2W) or every 3 weeks (Q3W), which is different from the current PBS listing of 2 mg/kg Q3W with a maximum amount of 200 mg. Trial KN006 did not state the maximum allowable dose, implying that the doses used in KN006 may have been substantially higher than the currently approved dose in Australia. Any differences in dosing between the trial and clinical practice could potentially lead to differences in the effectiveness and safety of pembrolizumab. However, the PBAC has previously considered that the evidence suggests, but does not guarantee, that there were no important differences in effectiveness or safety between the 2 mg/kg and 10 mg/kg dosing regimens for treatment of metastatic melanoma (para 7.7, Pembrolizumab,

PSD, March 2015). The Australian Product Information also states that patients receiving up to 10 mg/kg dose had a similar safety profile to that seen in patients receiving 2 mg/kg (p26 of Keytruda Product Information).

Comparative effectiveness

6.15 The PFS and OS results relevant to the BRAF mutation positive treatment naïve subgroups in KN006 and CM067 are summarised in Table 4 and Table 5.

Table 4: Summary of survival outcomes across the relevant treatment subgroups in the randomised trials

	KN006 BRAF mutant Rx naïve subgroup		CM067 BRAF mutant Rx naïve subgroup	
	Pembrolizumab N=108	Ipilimumab N=55	Ipilimumab N=100	Nivolumab N=98
Progression-free survival				
Median PFS, months (95% CI)	14.4 (7.0, 21.5)	4.2 (2.9, 8.3)	NR	5.6 (2.8, 9.5)[a]
PFS at landmark months, KM % (95% CI)				
24 months	34.7%	15.8%	NR	30%[a]
36 months	31.3%	11.3%	NR	23%[a]
48 months	28.6%	9.0%	10%	23%
Overall survival				
Median OS, months (95% CI)	NR (36.1, NR)	26.2 (16.0, NR)	24.6 (17.9, 31.0)	45.5 (26.4, NR)
PFS at landmark months, KM% (95% CI)				
24 months	69.0%	52.7%	NR	NR
36 months	60.1%	46.5%	NR	NR
48 months	53.9%	40.2%	46%	50%
60 months	40.2%	38.1%	30%	33%

CI = confidence interval; KM = Kaplan-Meier; NR = not reached; OS = overall survival; PFS = progression free survival; Rx = treatment.
[a] From Table 5, p15, nivolumab + ipilimumab, PBAC Public Summary Document (PSD), November 2019.
Source: Table compiled during the evaluation based on Table 2.6-1 and 2.6-2, p39 and p42 of the submission.

Table 5: Summary of results of the indirect comparison of pembrolizumab versus nivolumab using ipilimumab as the common reference in the target population

	KN006	CM067	Indirect Comparison (95% CI)	p-value
	Pembro vs. Ipi, HR (95% CI)	Nivo vs Ipi, HR (95% CI)		
OS	0.70 (0.44, 1.11)	0.63 (0.44, 0.90)	1.11 (0.62, 1.99)	0.7240
PFS	0.62 (0.42, 0.91)	0.73 (0.52, 1.01)	0.85 (0.51, 1.41)	0.5298

CI = confidence interval; HR = hazard ratio; Ipi = ipilimumab; Nivo = nivolumab; OS = overall survival; Pembro = pembrolizumab; PFS = progression free survival.
Source: Table 2.6-6, p46 of the submission.

6.16 The ESC noted in the KN006 trial that pembrolizumab was statistically significantly better than ipilimumab in terms of PFS, but not in terms of OS, whereas in the CM067 trial nivolumab was statistically significantly better than ipilimumab in terms of OS, but not in terms of PFS.

6.17 The submission claimed non-inferiority of pembrolizumab versus nivolumab for OS and PFS based on the non-significant p-values derived from indirect comparisons of survival hazard ratios. However, the PBAC Guidelines state that lack of a statistically significant difference between the proposed medicine and the comparator does not adequately establish non-inferiority (section 2.4.5, p47 of PBAC Guidelines version 5, 2016).

6.18 The upper 95% confidence intervals of 1.41 for PFS and 1.99 for OS are substantially higher than 1, and likely higher than any reasonable non-inferiority margin. The PSCR noted that the upper confidence bounds were high, but stated that this was due to the use of subgroups and the lack of power associated with the comparison between pembrolizumab and nivolumab.

6.19 The submission claimed that non-inferiority in efficacy was demonstrated as the median OS for pembrolizumab (not reached) was no less than nivolumab (45.5 months) and the 5-year survival rate of pembrolizumab (50.8%) was at least as high as for nivolumab (46.0%). The evaluators considered that this argument was flawed as the indirect comparisons consider the difference in survival between pembrolizumab and ipilimumab and separately between nivolumab and ipilimumab, not between pembrolizumab and nivolumab directly. The pre-PBAC response reiterated the statements made in the submission regarding median overall survival and survival rates at five years, adding that the hazard ratios for overall survival were also similar (pembrolizumab HR = 0.70; nivolumab HR = 0.63)

6.20 The submission further argued that the PBAC had previously accepted nivolumab to be non-inferior to pembrolizumab based on indirect comparisons using ipilimumab as the common reference (para 7.5, Nivolumab, PSD, November 2015).

6.21 Overall, the ESC were concerned that the upper 95% confidence interval for OS, which indicated up to twice the hazard of death with pembrolizumab compared to nivolumab, did not demonstrate non-inferiority between pembrolizumab and nivolumab.

6.22 The PBAC noted that neither KN006 nor CM067 were adequately powered to examine in-trial differences in the BRAF mutant subgroups or between trial differences, and considered that the wide confidence intervals of the indirect analyses were likely due to the fact that the analyses were based on a "subgroup of a subgroup".

6.23 The indirect comparison of overall survival did not consider the impact of subsequent treatments on survival in the KN006 and CM067 trials. As noted above in paragraph 6.8, a greater proportion of patients in the BRAF mutant subgroup of KN006 received subsequent treatments in the ipilimumab control group (79%) compared to the two pembrolizumab arms (54%). Although the PSCR provided additional information suggesting that the proportions of patients in the CN067 trial who received subsequent therapy were similar, the proportions of patients in the BRAF mutant subgroup receiving subsequent therapies was unknown. The ESC considered that imbalances in subsequent treatments could affect the hazard ratios.

Comparative harms

6.24 A summary of the indirect comparison of key adverse events occurring in the BRAF mutation positive subgroup of trial KN006 and the total intention to treat population of trial CM067 is presented in Table 6.

6.25 The submission used safety data from the total population of CM067, noting that the safety data from the BRAF mutation positive treatment naïve subgroup of CM067 was not publicly available. The total CM067 population was compared with the BRAF mutant population of KN006 to calculate relative risks associated with adverse events.

Table 6: Indirect comparison of adverse events from KN006 (BRAF mutant Rx naïve subgroup) and CM067 (ITT population)

	KN006 BRAF mutant Rx naïve population	CM067 Total population	Indirect comparison
	Pembro vs. Ipi, RR (95% CI)	Nivo vs Ipi, RR (95% CI)	RR, (95% CI)
Adverse events			
Total (drug-related)	1.06 (0.91, 1.23)	1.00 (0.94,1.07)	1.06 (0.90, 1.25)
Grade 3-5 (drug-related)	0.67 (0.33, 1.35)	0.84 (0.64,1.10)	0.80 (0.38, 1.70)
Discontinuations due to AEs	0.79 (0.27, 2.28)	0.85 (0.57,1.25)	0.93 (0.30, 2.90)
Diarrhoea (Grade 3-5)	0.49 (0.03, 7.69)	0.50 (0.23, 1.09)	0.98 (0.05, 17.46)
Colitis (Grade 3-5)	0.20 (0.04, 0.98)	0.33 (0.15, 0.73)	0.61 (0.10, 3.61)

AEs = adverse events; CI = confidence interval; Ipi = ipilimumab; ITT= intention to treat; Nivo = nivolumab; Pembro = pembrolizumab; RR = relative risk; Rx= treatment.
Source: Table 2.6-7, p47 of the submission.

Benefits/harms

6.26 A benefits/harms table was not presented as the submission claimed non-inferiority.

Clinical claim

6.27 The submission described pembrolizumab as non-inferior in terms of effectiveness and safety compared with nivolumab. The ESC considered that the claim of non-inferior safety was supported, but that the claim of non-inferior efficacy was not adequately supported given that:

- No pre-defined non-inferiority margins were nominated and the upper 95% confidence intervals for the PFS and OS hazard ratios exceeded unity by substantial margins.
- The indirect comparisons were amenable to high risk of bias and considerable confounding, e.g. due to possible imbalances in subsequent treatments.

6.28 The PBAC considered that the claim of non-inferior comparative effectiveness between pembrolizumab and nivolumab was uncertain but likely to be reasonable.

6.29 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.30 The submission presented a cost-minimisation analysis of pembrolizumab compared to nivolumab.

6.31 The equi-effective doses were estimated as:

Pembrolizumab 200 mg every 3 weeks = nivolumab 360 mg every 3 weeks

6.32 The equi-effective doses were based on the cited evidence within the two randomised trials KN006 and CM067 and the assumption that the mean duration of therapy is equal for pembrolizumab and nivolumab. The PSCR noted that the PBAC has previously accepted the durations of pembrolizumab and nivolumab therapy to be equal when considering pembrolizumab as a second-line treatment for BRAF mutant patients and as a first-line treatment for BRAF wild type patients. The ESC considered that the equi-effective doses were appropriate. The ESC considered that the assumption that the mean durations of therapy for pembrolizumab and nivolumab were equal was uncertain given that there was uncertainty surrounding whether pembrolizumab and nivolumab were non-inferior in terms of PFS due to the high upper 95% confidence limit of the hazard ratio.

6.33 DUSC has previously considered treatment duration data from the Department of Human Services (DUSC May 2018 Public Research Document, Medicines for the treatment of melanoma). This indicates a similar duration on treatment in second line treatment (mean 142 days for pembrolizumab, compared to 137 days for nivolumab); but this is not the case in first line therapy (mean 276 days for pembrolizumab, compared with 239 days for nivolumab). However, this data is uncertain given the low number treated with nivolumab (n=7), relative to pembrolizumab (n=586) (Table 7 of the DUSC May 2018 Public Research Document, Medicines for the treatment of melanoma).

6.34 The economic evaluation was based on the administration of:

Pembrolizumab 200mg every 3 weeks and nivolumab 480 mg every 4 weeks.

Drug cost/patient/year

6.35 The submission proposed the cost of pembrolizumab, based on the published approved ex-manufacturer price (AEMP) of nivolumab, as:

- $129,751.41 per patient per year, for 200 mg administered every 3-weeks.

Estimated PBS usage & financial implications

6.36 This submission was not considered by DUSC.

6.37 The submission employed an epidemiological approach to estimate the usage and financial implications for all PD-1 inhibitors (including, but not limited to pembrolizumab) as first line therapy for BRAF mutation positive patients, relative to existing BRAF/MEK inhibitors. This was inconsistent with the clinical evidence and economic analysis presented in the submission, which focused on pembrolizumab compared to nivolumab.

6.38 The PSCR provided an updated budget impact model to reflect the cost minimisation approach. The new model included data on the incidence of melanoma, removed a sub-population (20% of expected incidence) predicted to receive nivolumab and ipilimumab combination therapy and assumed a 50%/50% market share split between pembrolizumab and nivolumab. The revised model estimates no additional cost to the

PBS, which the ESC considered appropriate if the assumption of equal duration of treatment for pembrolizumab and nivolumab was accepted.

Table 7: Revised net financial implication of listing pembrolizumab on the PBS for first-line use in BRAF mutant patients with unresectable or metastatic melanoma, as presented in the PSCR (published prices)

	2020	2021	2022	2023	2024	2025
Patients receiving 1st line PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of 1st line PEMBRO	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost offsets due to reduced 1st line use of NIVO	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS	$0	-$2	$1	-$1	$2	$0

NIVO = nivolumab; PBS = Pharmaceutical Benefits Scheme; PEMBRO = pembrolizumab; PSCR = Pre-Sub-Committee Response; RPBS = Repatriation Pharmaceutical Benefits Scheme

Source: Table 3, p6 of the PSCR and BI Model – 1L BRAF_mutant_UPDATED – Excel model

Financial Management – Risk Sharing Arrangements

6.39 The pre-PBAC response stated that a cap uplift associated with the listing of PD-1 inhibitors for first-line use in patients with BRAF mutant unresectable or metastatic Stage III or IV melanoma was expected. The pre-PBAC response also claimed that the existing melanoma deed was based on patient numbers that are significantly less than the eligible PBS population.

6.40 The PBAC recalled that it reviewed the RSA of the PD-1 inhibitors across the adjuvant and unresectable or metastatic melanoma settings as part of the consideration of the November 2019 nivolumab submissions. The PBAC noted that the accepted RSA included a growth factor for the forward estimates, encompassed the entire melanoma market and consisted of subsidisation caps beyond which [redacted]% rebates would apply.

Quality Use of Medicines

6.41 The submission noted that clinicians would need to be educated about changes to the restriction for pembrolizumab use to include first line use in patients with BRAF positive unresectable Stage III or IV melanoma.

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

7 PBAC Outcome

7.1 The PBAC recommended the extension of the PBS listing for pembrolizumab to allow its use as a first-line therapy in the treatment of BRAF V600 mutant Stage III or Stage IV unresectable or metastatic melanoma. The PBAC considered that pembrolizumab would be cost-effective in this population if it was cost-minimised to nivolumab, which was recommended for the same indication in November 2019 and subsequently listed on the PBS on 1 March 2020. In addition, the PBAC recommended that pembrolizumab be included in the risk-sharing arrangement (RSA) agreed for nivolumab in the treatment of melanoma.

7.2 In terms of the clinical place in therapy, the PBAC recalled that it had previously restricted the use of pembrolizumab in patients with BRAF mutant unresectable or metastatic melanoma to those patients who had progressed following treatment with a BRAF±MEK inhibitors. The PBAC recalled that it had recommended nivolumab monotherapy and nivolumab in combination with ipilimumab as first-line therapies for these patients in November 2019. The PBAC noted that guidelines state that first-line systemic therapy should be individualised, with clinical factors dictating preference for use of BRAF-targeted treatment or immunotherapy.

7.3 The PBAC considered that nivolumab was the appropriate comparator for pembrolizumab as first-line therapy in BRAF mutant unresectable or metastatic melanoma.

7.4 The PBAC noted that the submission was based on an indirect comparison of subgroups of patients from the KN006 (pembrolizumab) and CM067 (nivolumab) trials in treatment naïve, BRAF mutant patients with unresectable or metastatic melanoma. Ipilimumab was the common comparator.

7.5 The PBAC considered, based on the available evidence for pembrolizumab and nivolumab for the treatment of melanoma, that the claim of non-inferior efficacy between pembrolizumab and nivolumab was uncertain but likely to be supported by the data.

7.6 In terms of comparative harms, the PBAC considered that pembrolizumab was non-inferior compared to nivolumab.

7.7 The PBAC noted that the submission presented a cost-minimisation analysis comparing pembrolizumab with nivolumab.

7.8 The PBAC noted that the durations of treatment for pembrolizumab and nivolumab were assumed to be equal, and that both are given until disease progression. The PBAC considered that this was appropriate. The PBAC considered that the equi-effective doses were:

Pembrolizumab 200 mg every 3 weeks = Nivolumab 360 mg every 3 weeks

7.9 The PBAC noted that the PSCR provided an updated estimate of the financial impact of the revised pembrolizumab listing which indicated that there would be no additional cost to the PBS. The PBAC considered that this was appropriate as it recalled that in November 2019 it advised that the restriction changes for nivolumab and ipilimumab should result in no additional costs to the PBS/RPBS.

7.10 The PBAC recalled that it reviewed the RSA of the PD-1 inhibitors across the adjuvant and unresectable or metastatic melanoma settings as part of the consideration of the November 2019 nivolumab submissions. The PBAC noted that the accepted RSA encompassed the entire melanoma market and consisted of subsidisation caps beyond which 100 per cent rebates would apply. The PBAC recommended that pembrolizumab join the revised RSA.

7.11 In terms of the Special Pricing Arrangement (SPA) for pembrolizumab, the PBAC considered that the price of pembrolizumab should be consistent across the adjuvant and unresectable or metastatic settings with the agreed weighted pricing of nivolumab.

7.12 For patients who receive a PD-1 inhibitor in the adjuvant setting the PBAC advised that pembrolizumab could only be used as retreatment in the unresectable or metastatic setting if patients had completed 12 months of adjuvant therapy and remained recurrence free for six months following completion of adjuvant therapy.

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

7.14 The PBAC recommended that the Early Supply Rule should not apply to the listing of pembrolizumab combination therapy.

7.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because the availability of pembrolizumab as a first-line treatment option for patients with BRAF mutant unresectable or metastatic melanoma was not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over nivolumab, and not expected to address a high and urgent unmet clinical need, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

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

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing unresectable Stage III or Stage IV malignant melanoma listings (by retaining and amending Initial 2; delete Initial 1) to read as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
PEMBROLIZUMAB Injection	10493G (Public) 10475H (Private)	200 mg	5	Merck Sharp & Dohme (Australia) Pty Ltd
Available brands				
Keytruda (pembrolizumab 100 mg/4 mL injection, 4 mL vial)				

Category/Program: Section 100 Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☒ Authority Required - Streamlined (10088)
Administrative Advice: No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply. Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.

Indication: Unresectable Stage III or Stage IV malignant melanoma
Treatment Phase: Initial treatment – 3 weekly treatment regimen
Clinical criteria:
▪ Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma **AND** ▪ Patient must not have experienced disease progression whilst on adjuvant PD-1 inhibitor treatment or disease recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment if treated for resected Stage IIIB, IIIC, IIID or IV melanoma **AND** ▪ The treatment must be the sole PBS-subsidised therapy for this condition **AND** ▪ The treatment must not exceed a total of 6 doses under this restriction
Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.

For the continuing restriction, apart from updating the treatment phase description, no changes are required for pembrolizumab's 'continuing treatment' criteria in unresectable Stage III or Stage IV malignant melanoma, as there is no BRAF specific language.

8.2 Add new 6-weekly treatment listing as per recommendation from the Public Summary Document of item 6.13 pembrolizumab of this meeting as follows:

Name, Restriction, Manner of administration and form	**PBS item code**	**Max. Amount**	**№.of Rpts**	**Manufacturer**
PEMBROLIZUMAB Injection	NEW (Public) NEW (Private)	400 mg	2	Merck Sharp & Dohme (Australia) Pty Ltd
Available brands				
Keytruda (pembrolizumab 100 mg/4 mL injection, 4 mL vial)				

Category/Program: Section 100 Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☒ Authority Required - Streamlined (NEW CODE)
Administrative Advice: No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply. Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.
Indication: Unresectable Stage III or Stage IV malignant melanoma
Treatment Phase: Initial treatment – 6 weekly treatment regimen
Clinical criteria: ▪ Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma **AND** ▪ Patient must not have experienced disease progression whilst on adjuvant PD-1 inhibitor treatment or disease recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment if treated for resected Stage IIIB, IIIC, IIID or IV melanoma **AND** ▪ The treatment must be the sole PBS-subsidised therapy for this condition **AND** ▪ The treatment must not exceed a total of 3 doses under this restriction
Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
PEMBROLIZUMAB Injection	NEW (Public) NEW (Private)	400 mg	3	Merck Sharp & Dohme (Australia) Pty Ltd
Available brands				
Keytruda (pembrolizumab 100 mg/4 mL injection, 4 mL vial)				

Category/Program: Section 100 Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☒ Authority Required - Streamlined (NEW CODE)
Administrative Advice: No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply. Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.
Indication: Unresectable Stage III or Stage IV malignant melanoma
Treatment Phase: Continuing treatment – 6 weekly treatment regimen
Clinical criteria: ▪ The treatment must be the sole PBS-subsidised therapy for this condition **AND** ▪ Patient must have previously been issued with an authority prescription for this drug for this condition **AND** ▪ Patient must have stable or responding disease

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

MSD is pleased with the positive recommendation by the PBAC for this indication, as is working with the Department to try to achieve a PBS listing as soon as possible.