

7.08 PEMBROLIZUMAB, 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 resubmission requested a Section 100 (Streamlined), Efficient Funding of Chemotherapy listing for pembrolizumab as adjuvant treatment of patients with completely resected Stage III malignant melanoma, at high risk of recurrent disease. High risk was defined as Stage IIIA (> 1 mm), IIIB, IIIC or IIID disease based on the 8th edition of the American Joint Committee on Cancer (AJCC) melanoma staging system. The proposed patient population was updated in the pre-Sub-Committee Response (PSCR) to include those with Stage IIIB, IIIC or IIID disease only.
- 1.2 Pembrolizumab was previously considered for the adjuvant treatment of patients with completely resected Stage III malignant melanoma at the November 2018 PBAC meeting. The submission was rejected on the basis of uncertainty in the magnitude of the clinical benefit and a highly uncertain incremental cost-effectiveness ratio (ICER). In addition, the estimated financial impact was very high and uncertain.
- 1.3 The requested listing was based on a cost-utility analysis of pembrolizumab compared with placebo.
- 1.4 The key components of the clinical issues addressed by the submission are summarised below.

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

Component	Description
Population	Patients with completely resected Stage III malignant melanoma, at high risk of recurrent disease; defined as Stage IIIA (>1 mm), IIIB, IIIC or IIID disease based on the 8th edition of the AJCC staging system. This was updated in the PSCR to exclude all patients with Stage IIIA disease.
Intervention	Pembrolizumab 200 mg intravenous infusion every 3 weeks, maximum of 18 cycles (adjuvant therapy)
Comparator	Main comparator: current standard of care (placebo) Supplementary (near market) comparators: nivolumab; dabrafenib+trametinib (BRAF mutation positive)
Outcomes	Primary outcome: recurrence free survival (RFS) Secondary outcomes: distant metastasis free survival (DMFS), overall survival (OS) Safety: all-cause and treatment-related adverse events
Clinical claim	In patients with resected Stage III melanoma, pembrolizumab is superior to placebo in terms of efficacy. The resubmission claimed that the reduced risk of recurrence, reduced risk of distant metastasis and fewer deaths observed in the trial are expected to translate to an overall improvement in survival. In terms of safety, pembrolizumab has inferior but manageable safety.

AJCC = American Joint Committee on Cancer; PSCR = pre-Sub-Committee response
Source: Table 1-1, pp11-12 of the resubmission

2 Requested listing

Suggested additions to the proposed restrictions are in italics, suggested deletions are in strikethrough.

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
PEMBROLIZUMAB 100 mg/4 mL infusion, 1 x 4 mL vial	200 mg	5	Published price: \$9,024.44 (Public hospital) \$9,185.54 (Private hospital) Effective price: \$ [REDACTED] (Public hospital) \$ [REDACTED] (Private hospital)	KEYTRUDA® Merck Sharp & Dohme (Australia) Pty Limited

Source: Table 1.4-1, p.22 of the resubmission

Category/program	Section 100 (Public/Private), Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Resected Stage IIIB, Stage IIIC or Stage IIID
Condition:	Malignant melanoma
PBS Indication:	Resected Stage IIIB, Stage IIIC or Stage IIID malignant melanoma
Treatment phase:	Initial
Restriction:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED) <input checked="" type="checkbox"/> Authority Required (Telephone)
Clinical criteria:	The treatment must be adjuvant to complete surgical resection, AND The patient must be at high risk of recurrence following complete surgical resection, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND The patient must have a WHO performance status of 0 or 1, AND The patient must not have received prior PBS-subsidised treatment with a programmed cell death-1 (PD-1) inhibitor for this condition.
Treatment criteria:	The treatment must be initiated commence within 12 weeks of surgical complete resection, unless delay is necessary due to post-surgery recovery; AND Treatment must not exceed a maximum duration of 12 months (18 cycles at a dose of 200 mg every 3 weeks) (initial and continuing therapy) under this restriction. <i>The treatment is not PBS-listed for mucosal or ocular melanoma</i>
Notes:	<i>Complete resection of Stage III disease must be documented on the surgical and pathology reports. No increase in the maximum quantity or number of units or number of repeats will be authorised. Special Pricing Arrangements apply.</i>

Category/program	Section 100 (Public/Private), Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Resected Stage IIIB, Stage IIIC or Stage IIID
Condition:	Malignant melanoma
PBS Indication:	Resected Stage IIIB, Stage IIIC or Stage IIID malignant melanoma
Treatment phase:	Continuing
Restriction:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED) <input checked="" type="checkbox"/> Authority Required (Telephone)

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Clinical criteria:	The patient must have previously been issued with an authority prescription to receive for this drug for this condition in the adjuvant setting <i>adjuvant treatment following complete surgical resection</i> , AND The treatment must be the sole PBS-subsidised therapy for this condition, AND The patient must not have evidence of recurrence. AND
Treatment criteria:	The treatment is not PBS listed for mucosal or ocular melanoma Treatment must not exceed a maximum duration of 12 months (18 cycles at a dose of 200 mg every 3 weeks) (initial and continuing therapy) under this restriction.
Notes:	No increase in the maximum quantity or number of units or number of repeats will <i>may</i> be authorised. <i>Special Pricing Arrangements apply</i>

Category/program	Section 100 (Public/Private), Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Resected Stage IIIB, Stage IIIC or Stage IIID
Condition:	Malignant melanoma
PBS Indication:	Resected Stage IIIB, Stage IIIC or Stage IIID malignant melanoma
Treatment phase:	Grandfathering treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED) <input checked="" type="checkbox"/> Authority Required (Telephone)
Clinical criteria:	Patient must have <i>previously</i> received non-PBS treatment with this drug for <i>adjuvant treatment following complete surgical resection</i> this condition in the adjuvant setting prior to [date of PBS listing], AND The patient must be at high risk of recurrence following complete surgical resection, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND The patient must have a WHO performance status of 0 or 1, AND The patient must not have evidence of recurrence.
Treatment criteria:	The treatment is not PBS listed for mucosal or ocular melanoma Treatment must not exceed a maximum duration of 12 months (18 cycles at a dose of 200 mg every 3 weeks) (initial and continuing therapy) under this restriction.
Notes:	No increase in the maximum quantity or number of units or number of repeats will <i>may</i> be authorised. <i>Special Pricing Arrangements apply</i>

Pembrolizumab/nivolumab	
Category/program	Section 100 (Public/Private), Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial treatment 3
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for this condition in the unresectable Stage III or Stage IV setting; AND Patient must have completed 12 months of prior therapy with a PD-1 inhibitor for this condition in the resected stage III <i>adjuvant</i> setting without a recurrence while on treatment; AND Patient must not have experienced a recurrence within 6 months of completing prior therapy with a PD-1 inhibitor in the resected stage III setting; AND The treatment must be the sole PBS-subsidised therapy for this condition; AND

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	The patient must have a WHO performance status of 0 or 1 The treatment must not exceed a total of 6 doses at a maximum dose of 2 mg per kg every 3 weeks. The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Notes:	No increase in the maximum quantity repeats may be authorised. Special Pricing Arrangements apply

- 2.1 The proposed Special Pricing Arrangement (SPA) for pembrolizumab in the adjuvant melanoma setting (█% discount applied to the published ex-manufacturer price) is unchanged from the November 2018 submission. In addition, the resubmission proposed a Risk-Sharing Arrangement (RSA) for the use of pembrolizumab in the adjuvant setting (see paragraphs 6.75 to 6.77).
- 2.2 The PBAC has indicated that restrictions for adjuvant therapies for completely resected Stage III melanoma should exclude patients with Stage IIIA disease as classified using the 8th edition of the AJCC staging system (Correspondence from the PBAC to the MSAC, 29 April 2019). The PSCR agreed with the proposed change to the PBS indication to limit treatment to patients with Stage IIIB, IIIC or IIID disease only. The PBAC considered this change was reasonable.
- 2.3 In previous considerations of melanoma treatments in the adjuvant setting, the PBAC has indicated that exclusion of patients with ocular melanoma was inappropriate.
- 2.4 The resubmission proposed a restriction for retreatment with pembrolizumab for patients who progress to unresectable Stage III or Stage IV malignant melanoma after completing twelve months of treatment with pembrolizumab and remaining recurrence free for at least six months following completion of treatment. The PBAC considered that this was appropriate. As in the November 2018 submission, no clinical evidence was presented supporting retreatment with pembrolizumab.
- 2.5 The PBAC advised that an Authority Required (Telephone) listing would be appropriate for both the initial and continuing treatment phases to prevent leakage to patients with Stage IIIA disease and to ensure treatment was capped at 12 months.

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

3 Background

Registration status

- 3.1 Pembrolizumab was approved for registration by the TGA on 17 December 2018 as:
"Monotherapy for the adjuvant treatment of patients with melanoma with lymph node involvement who have undergone complete resection."
- 3.2 Pembrolizumab is also listed on the Australian Register of Therapeutic Goods (ARTG) as monotherapy for unresectable or metastatic melanoma (Stage III, Stage IV), monotherapy and combination therapy with methotrexate for non-small cell lung

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carcinoma (NSCLC), recurrent or metastatic head and neck cancer, relapsed or refractory classical Hodgkin Lymphoma (cHL), refractory primary mediastinal B-cell lymphoma (PMBCL), and locally advanced or metastatic urothelial carcinoma.

Previous PBAC consideration

Table 2: Summary of outstanding matters of concern

Component	Matter of Concern to the PBAC Nov 2018	Approach in the resubmission
Clinical issues		
Requested restriction (Stage IIIA patients)	The proposed PBS listing included all resected Stage III patients, but Stage IIIA ≤ 1 mm patients were not represented in the clinical trial population [para.7.6].	Proposed PBS listing restricted to high risk Stage III patients; i.e. excluding Stage IIIA ≤ 1 mm. This was updated in the PSCR to exclude all Stage IIIA patients.
Staging subgroups	The prognosis for Stage III patients varied widely by staging subgroups and the appropriate population for treatment had not been identified [para.7.1].	Results were presented for the AJCC 8th edition staging system subgroups (Stage IIIA > 1 mm to Stage IIID).
AJCC staging criteria	Patients categorised using the AJCC 8th edition criteria (current clinical practice) may have a more favourable survival profile across Stages IIIA, IIIB, and IIIC disease compared with patients with similar stage groupings in the AJCC 7th edition (used in the clinical trial and November 2018 submission). The appropriate patient population for treatment with adjuvant pembrolizumab remained unclear [para.7.7].	Results were presented using the AJCC 8th edition staging system for the total trial population and Stage III subgroup analyses.
Treatment effect	The magnitude of the recurrence free survival treatment effect was highly uncertain and the impact on overall survival was unknown due to immaturity of the clinical trial data (median recurrence free survival for pembrolizumab had not been reached) [para.7.8].	Unchanged. The resubmission used the same trial data considered at the November 2018 meeting. Results for overall survival not expected [REDACTED].
Safety	The submission did not make a safety claim. The PBAC considered pembrolizumab was inferior to placebo in terms of safety in the adjuvant treatment of completely resected Stage III melanoma [para.7.9].	The clinical claim was amended to inferior but manageable safety.
Retreatment	The submission proposed retreatment with pembrolizumab in the unresectable setting. The PBAC was concerned by lack of comparative evidence for, and the potential unknown downstream consequences of, retreatment with anti-PD-1 therapies in terms of efficacy, safety and cost-effectiveness [para.7.4].	The resubmission claimed that retreatment is anticipated in a small proportion of patients (approximately 6%). Retreatment data are expected in [REDACTED].
Economic issues		
Population	The model population, which was informed by the trial population, had a poorer prognosis than the likely PBS population [para.7.10].	The population was reanalysed using the AJCC 8th edition staging system, and includes separate analyses by stage subgroup (Stage IIIA > 1 mm, IIIB, IIIC and IIID).

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Component	Matter of Concern to the PBAC Nov 2018	Approach in the resubmission
Modelled OS	Overall survival in both arms of the model was low when compared to melanoma specific survival probabilities presented in the AJCC 8th edition [para.7.10].	The resubmission provided additional analyses comparing modelled outcomes with comparable published outcomes, including a comparison with melanoma specific survival by substage presented in the AJCC 8th edition, based on the International Melanoma Database. The ESC considered that modelled overall survival estimates not only remained underestimated, but were clinically implausible.
Data maturity	The modelled data were based on immature RFS trial evidence (median RFS for pembrolizumab had not yet been reached); no overall survival data were available [para.7.10].	No change. No additional follow up data are available.
RFS to OS surrogacy	Quantification of the relationship between RFS and overall survival was uncertain, and the impact of treatment for recurrence on this relationship unknown [para.7.10].	No changes made to the economic model. No additional follow up data are available. A rationale supporting the relationship of RFS to OS in the current adjuvant melanoma context was provided. The pre-PBAC response stated that every available source was presented, and that there was a very clear biological basis for the relationship, including that RFS and DMFS always precede OS.
Post-progression inputs	<p>Relevance of post-recurrence inputs for the adjuvant pembrolizumab arm, given that there was no efficacy or safety data for patients who received a PD-1 inhibitor in both the adjuvant and unresectable settings [para.7.10].</p> <p>In addition, the cost and effectiveness of treatments post-progression were based on progression free survival and overall survival curves derived from external evidence (KN006 and a network meta-analysis).</p>	<p>No major changes were made to the economic model. No additional follow up data are available. Part 2 of KN054 will provide direct evidence of effectiveness in this clinical scenario (PD-1 inhibitor in both settings).</p> <p>The resubmission included sub-states within the distant metastases health state in order to explore the impact of treatments for advanced melanoma. New modelled substates were designed according to the patient's eligibility for treatment in the advanced setting: rechallenge-eligible (can receive pembrolizumab in the advanced setting, subject to specific criteria for retreatment in line with proposed restriction); immunotherapy-eligible (no restriction on receiving treatment in the advanced setting) or immunotherapy-ineligible (cannot receive pembrolizumab or nivolumab in the advanced setting).</p>
Financial issues		
Incident Population	The estimated incident population was based on an old data source [para.6.58].	The financial model used a more recent data source to estimate the proportion of incident melanoma patients diagnosed with Stage III melanoma (8.5%; NSW Cancer Registry 2010).
Cost-offsets	Cost-offsets for post-progression treatment applied in the economic model were not applied in the financial estimates [para.7.11].	Cost offsets were included in the financial model. The extent of cost offsets expected for adjuvant patients was calculated by estimating the proportion of patients who no longer receive anti-PD1 therapy in the metastatic setting and the proportion of patients who no longer progress to Stage IV and receive treatment because of pembrolizumab treatment in the adjuvant setting.

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Component	Matter of Concern to the PBAC Nov 2018	Approach in the resubmission
Administrations per patient	The average number of administrations per patient (████ per year) overestimated dose intensity and cost per patient [para.7.12].	The relative dose intensity in KEYNOTE-054 was 99.7%. The resubmission stated that applying this factor to the estimates would not materially affect the treatment duration assumptions and so dose intensity was not included in the modelled financial estimates.
Uptake rate	Uptake rate of 85% was considered high [para.7.12].	The resubmission applied a lower uptake rate for Stage IIIA patients (50%) based on prognosis and in order to exclude patients with tumour size ≤1 mm, however maintained that the 85% uptake rate was appropriate for the other stages given that the population are typically young and otherwise healthy but with a high risk of recurrence.

AJCC = American Joint Committee on Cancer; DMFS = distant metastases free survival; OS = overall survival; PD-1 = programmed cell death-1; RFS = recurrence free survival

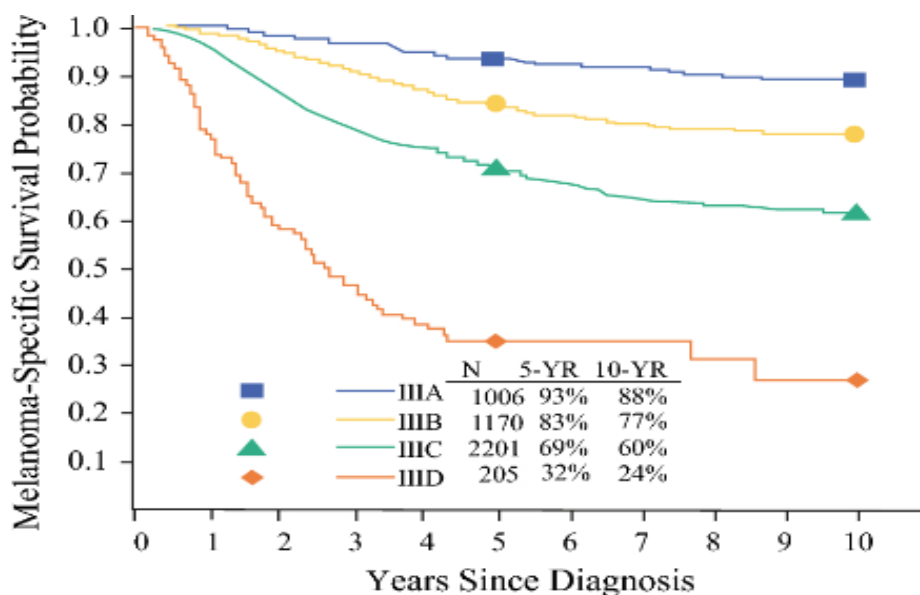
Source: Table 1.1-1, pp.1-3 of the resubmission

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

4 Population and disease

- 4.1 Melanoma is a skin cancer originating in pigment-producing melanocytes as a result of unrepaired DNA damage and/or other genetic mutation. Stage III disease includes patients with involvement of regional lymph nodes and/or the presence of in transit, satellite and/or micro satellite metastases.
- 4.2 The proposed eligible population in the resubmission is limited to patients with Stage III malignant melanoma at high risk of recurrence following complete surgical resection (i.e. Stage IIIA > 1 mm, Stage IIIB, Stage IIIC or Stage IIID, AJCC 8th edition). The exclusion of patients with Stage IIIA disease ≤ 1 mm (i.e. maximum diameter of largest metastatic deposit in sentinel node ≤ 1 mm) is consistent with the clinical trial population (Trial KN054). The use of the 8th edition of the AJCC melanoma staging system is consistent with Australian clinical practice.
- 4.3 The five year and ten year melanoma specific survival rates for Stage III disease, based on database analyses conducted for the AJCC 8th edition international melanoma database, are presented in Figure 1 below.

Figure 1: Survival probability for melanoma as reported by the AJCC 8th edition Stage III system



AJCC = American Joint Committee on Cancer; YR = year
Source: Gershenwald et al. (2018)

4.4 The ESC again noted the low risk of recurrence for patients with Stage IIIA disease.

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

5 Comparator

5.1 The PBAC accepted observation (placebo) as the appropriate main comparator at the November 2018 meeting (paragraph 7.3, Pembrolizumab Minutes, November 2018).

5.2 The resubmission also nominated nivolumab and dabrafenib/trametinib as near market comparators (unchanged from the November 2018 submission). Nivolumab (second submission) and dabrafenib/trametinib (first submission) were considered at the March 2019 PBAC meeting for adjuvant therapy to complete resected Stage III malignant melanoma, and minor submissions for both treatments were considered at the July 2019 PBAC meeting.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), health care

professionals (17) and organisations (4) via the Consumer Comments facility on the PBS website. The individual and health care professional comments described a range of benefits of treatment with adjuvant pembrolizumab including prolonged life, improved quality of life and few side effects.

- 6.3 The PBAC noted the advice received from i) Melanoma Tasmania, ii) Melanoma Patients Australia, and iii) Australian Melanoma Consumer Alliance and the Melanoma Research Victoria Consumer Reference Group, all which supported the listing of pembrolizumab for Stage III resected melanoma on the PBS.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the adjuvant pembrolizumab in Stage III melanoma submission, categorising it as one of the therapies of “highest priority for PBAC listing” on the basis of the Phase III clinical evidence provided by the KN054 trial. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab, which was a Grade A, which is the highest grade (out of C, and where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies), based on a comparison with placebo in the KN054 trial.¹

Clinical trials

- 6.5 The resubmission was based on Trial KN054 comparing pembrolizumab to placebo as adjuvant therapy in patients with complete resection of Stage III melanoma, the key study considered by the PBAC at the November 2018 meeting. The ESC noted that no new clinical evidence relevant to adjuvant therapy for Stage III melanoma was identified in the resubmission. The resubmission did present new *post hoc* overall (ITT) and Stage III subgroup analyses of the Trial KN054 patient data re-graded using the AJCC 8th edition staging system.
- 6.6 Supportive indirect comparisons between pembrolizumab (Trial KN054) and the near market comparators, nivolumab (CA238, Hemstock et al. 2019) and dabrafenib+trametinib (BRAF V600 positive; Study COMBI-AD, Hauschild et al. 2018), and one network meta-analysis of medicines used in the treatment of malignant melanoma (Lorenzi et al. 2018), were presented as attachments to the resubmission. The supportive indirect comparisons were updated from the November 2018 submission.
- 6.7 Details of the trials presented in the submission are provided in the table below.

¹ Cherny N, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefits scale, version 1.1. *Annals of Oncology*. 2017; 28: 2340-2366.

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Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials presented in the resubmission		
KN054 (NCT02362594)	Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group Eggermont, A, Blank C, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected Stage III melanoma. Bottomley A., Coens C., Blank C., Mandala M., Long G.V. et al. HRQoL results for pembrolizumab versus placebo after complete resection of high-risk Stage III melanoma from the EORTC 1325-MG/ Keynote 054 trial: An international randomized double-blind phase 3 trial (Abstract)	Report date: March 2018 <i>New England Journal of Medicine</i> 2018; 378:1789-1801 <i>Pigment Cell and Melanoma Research</i> 2019; 32(1):102
Randomised trials presented in supportive indirect comparisons in the resubmission		
CheckMate 238/ CA238	Weber, J., et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. Hemstock M, et al. Evaluating the relative efficacy of nivolumab versus placebo as adjuvant treatment for melanoma using multiple methods of indirect treatment comparison.	<i>New England Journal of Medicine</i> 2017; 377(19): 1824-1835 <i>Pigment Cell and Melanoma Research</i> 2019; 32(1):94
EORTC 18071/ CA029	Eggermont, A, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial.	<i>The Lancet Oncology</i> 2015; 16(5):522-530
COMBI-AD	Long, G., et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. Hauschild A, et al. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected BRAF V600-mutant Stage III melanoma.	<i>New England Journal of Medicine</i> 2017; 377:1813-1823 <i>Journal of Clinical Oncology</i> 10 Dec 2018; 36(35):3441–3449
Meta-analyses presented as supportive evidence in the resubmission		
Lorenzi et al. (2018)	Lorenzi M, et al. Systematic literature review and network meta-analysis of Pembrolizumab for the treatment of stage III melanoma: Technical report (2).	Precision Xtract, 2 June 2018

Source: Table 2.2-1, p.37 of the resubmission

6.8 The key features of the trials presented in the resubmission are summarised in the table below.

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Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Pembrolizumab vs placebo						
KN054	1,019	R, DB, MC, Phase III; 16 months follow up	Low	≥ 18 years Completely resected Stage III (>1 mm), IIIB, IIIC melanoma (AJCC 7 th)	RFS (DMFS, OS, QoL) ^a	Parametric functions fit to trial based transitions from recurrence free
Pembrolizumab vs nivolumab (supportive)						
CA238	906	R, DB, MC, Phase III; NIVO v IPI, 18 months follow up (minimum)	Low	≥ 15 years Completely resected Stage IIIB, IIIC and IV (AJCC 7 th)	RFS (DMFS, QoL)	Not used
CA029	951	R, DB, MC, Phase III; IPI v PBO, 2.7 years follow up	Low	≥ 18 years Completely resected Stage IIIA (>1 mm), IIIB, IIIC melanoma (AJCC 7 th)	RFS (DMFS, OS, QoL)	Not used
Pembrolizumab vs dabrafenib+trametinib (supportive)						
COMBI-AD	870	R, DB, MC, Phase III; DAB+TRAM v PBO 2.8 years follow up	Low	≥ 18 years Completely resected Stage IIIA, IIIB, IIIC melanoma (AJCC 7 th) BRAF V600 mutation positive	RFS (OS, DMFS)	Not used

DB = double blind; DAB+TRAM = dabrafenib+trametinib; DMFS = distant metastasis-free survival; IPI = ipilimumab; MC = multi-centre; NIVO = nivolumab; OS = overall survival; PBO = placebo; R = randomised; RFS = recurrence free survival

^a DMFS and OS outcome data were immature for formal survival analysis, but were presented for the October 2017 data cut-off

Source: Compiled during the evaluation

6.9 The redistribution of patients across substages in Trial KN054 after re-grading from the 7th to the 8th AJCC staging system is summarised in the table below.

Table 5: Trial KN054 post-hoc regrading of patients from AJCC 7th edition to AJCC 8th edition staging system

Per protocol AJCC 7 th edition	Trial KN054 restaged <i>post-hoc</i> by AJCC 8 th edition n (%)					
	Stage IIIA (> 1 mm)	Stage IIIB	Stage IIIC	Stage IIID	Unknown	Total (AJCC 7 th)
Pembrolizumab						
Stage IIIA (> 1 mm)	32 (6.2%)	29 (5.6%)	15 (2.9%)	0	4 (0.8%)	80 (15.6%)
Stage IIIB	9 (1.8%)	110 (21.4%)	109 (21.2%)	0	9 (1.8%)	237 (46.1%)
Stage IIIC	1 (0.2%)	25 (4.9%)	143 (27.8%)	19 (3.7%)	9 (1.8%)	197 (38.3%)
Total (AJCC 8th)	42 (8.2%)	164 (31.9%)	267 (51.9%)	19 (3.7%)	22 (4.3%)	514
Placebo						
Stage IIIA (> 1 mm)	35 (6.9%)	32 (6.3%)	13 (2.6%)	0	0	80 (15.8%)
Stage IIIB	5 (1.0%)	131 (25.9%)	83 (16.4%)	0	11 (2.2%)	230 (45.5%)
Stage IIIC	0	28 (5.5%)	120 (27.7%)	20 (4.0%)	7 (1.4%)	195 (38.6%)
Total (AJCC 8th)	40 (7.9%)	191 (37.8%)	236 (46.7%)	20 (4.0%)	18 (3.6%)	505
Haydu (2017) ^a	220 (4.8%)	2,007 (44.2%)	1,709 (37.6%)	104 (2.3%)	500 (11.0%)	4,540

AJCC = American Joint Committee on Cancer

^a Haydu et al. (2017), based on Melanoma Institute Australia database, all patients at Stage III melanoma diagnosis (AJCC 8th edition), regardless of resection, BRAF or PD-L1 status

Source: Table 2.4-4, p.49 of the resubmission; Table 4.1.2, p.8, Internal Report AJCC KN054; Haydu et al. (2017)

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- 6.10 The primary outcome of Trial KN054 was recurrence free survival. The resubmission acknowledged that the available RFS data for Trial KN054 were immature (i.e. median recurrence free survival for pembrolizumab had not been reached).
- 6.11 At the November 2018 meeting, the PBAC noted that recurrence free survival was the primary outcome of Trial KN054, but that overall survival is the most clinically relevant endpoint for evaluation of an anti-cancer medicine (paragraph 6.10, Pembrolizumab minutes, November 2018). The ESC, noting that early retreatment data was not expected to be available until [REDACTED] and a formal analysis of overall survival data might not be available [REDACTED], remained concerned by the immaturity of the data.
- 6.12 The ESC noted that no new information was presented regarding the use of recurrence free survival as a surrogate for overall survival and noted that the resubmission restated the arguments presented in the November 2018 submission and the November 2018 PSCR that were based on the Suciú et al (2018) validation study.
- 6.13 The resubmission also argued that the COMBI-AD trial comparing dabrafenib+trametinib to placebo for adjuvant treatment of patients with BRAF mutation positive Stage III melanoma (Long et al. 2017), supported the surrogacy of recurrence free survival to overall survival when the availability of downstream therapies in the metastatic setting was considered. While the comparison between pembrolizumab and dabrafenib+trametinib shows adjunctive therapy with pembrolizumab (PD-1 inhibitors) or dabrafenib+trametinib (BRAF-MEK inhibitors) provides some benefit to patients in terms of recurrence free survival compared to placebo, no link between the relative magnitude of recurrence free survival and overall survival benefit was demonstrated.
- 6.14 The ESC reiterated that the suitability of recurrence free survival as a surrogate for overall survival in the assessment of pembrolizumab as adjuvant therapy for resectable Stage III melanoma has not been established.
- 6.15 Quality of life outcomes for Trial KN054 were collected using the EORTC QLQ-C30 and EQ-5D-3L instruments, but results were not reported in the resubmission or the KN054 Clinical Study Report.

Comparative effectiveness

- 6.16 Results for recurrence free survival in Trial KN054 (ITT population) are presented for the AJCC 7th edition (pre-specified) and AJCC 8th edition (*post hoc*) staging system in Table 5 and Figure 2 below.

Table 6: Trial KN054 recurrence free survival by AJCC 7th and 8th edition staging system (ITT)

	Pembrolizumab N=514	Placebo N=505	Absolute difference ^a	HR (98.4% CI) ^a
Events, n (%)	135 (26.3%)	216 (42.8%)	16.5%	–
Survival rate (95% CI) ^b				
6 months	82.2% (78.6, 85.3)	73.3% (69.2, 77.0)	8.9%	–
12 months	75.4% (71.3, 78.9)	61.0% (56.5, 65.1)	14.4%	–
18 months	71.4% (66.8, 75.4)	53.2% (47.9, 58.2)	18.2%	–
AJCC 7th edition (data cut-off 2 Oct 2017)				
Median RFS (95% CI) months	Not reached (-, -)	20.4 (16.2, -)	–	0.57 (0.43, 0.74)
AJCC 8th edition (data cut-off 2 Oct 2017)				
Median RFS (95% CI) months	Not reached (-, -)	20.4 (16.2, -)	–	0.55 (0.42, 0.71)

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; RFS = recurrence free survival

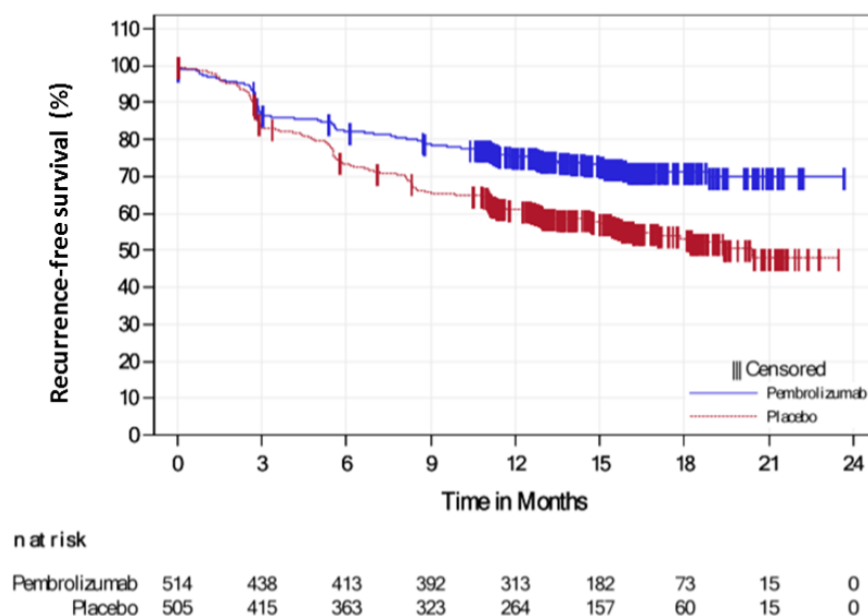
^a Pembrolizumab vs placebo. Treatment as covariate stratified by disease stage. Hazard ratio <1 favours pembrolizumab

^b From the product-limit (Kaplan-Meier) method for censored data

Note: New analyses shaded

Source: Table 2-20, p.78 of the resubmission

Figure 2: Trial KN054 Kaplan-Meier plot of recurrence free survival (ITT, AJCC 7th edition)



ITT = intention-to-treat

Source: Figure 2.5-1, p.79 of the resubmission

6.17 Patients in the pembrolizumab arm had statistically significantly longer recurrence-free survival compared to the placebo-treated patients (median not reached versus 20.4 months; HR = 0.57; 95% CI: 0.43, 0.74). The hazard ratio was slightly more favourable when the AJCC 8th edition staging system was used (HR = 0.55; 98.4% CI: 0.42, 0.71), due to differences in the distribution of patients across AJCC disease stages impacting the use of treatment stratified by staging as a covariate in the Cox regression model.

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6.18 Recurrence free survival in Trial KN054 remained immature, and the absolute magnitude of the treatment effect remains uncertain. PBAC concerns about the relative treatment effect and validity of the proportional hazards assumption identified at the November 2018 meeting were not addressed in the resubmission (paragraph 6.17, Pembrolizumab minutes, November 2018). The PSCR and pre-PBAC response noted that in checkpoint inhibitor studies there may be an initial delay in treatment effect, and while proportional hazards may not be present, the Cox proportional hazards model was insensitive to deviations from proportional hazards in selected studies (CA017, CA025, CA057, CA066, CA141, KN045 and KN024). The PSCR and pre-PBAC response also stated that as the economic model base case does not include the proportional hazards assumption this does not affect the cost-effectiveness assumptions.

6.19 Subgroup analyses by AJCC staging system are summarised in Table 7 below. The resubmission acknowledged that multiplicity adjustments were not made for subgroups by AJCC staging system.

Table 7: Trial KN054 recurrence free survival (RFS) subgroups by AJCC 7th and 8th edition staging system (ITT)

Stage	Treatment	N	Events, n (%)	Median RFS, months (95% CI)	RFS rate (month 6) % (95% CI) ^a	Hazard ratio (95% CI) ^b
AJCC 7th edition						
Stage IIIA >1 mm	Pembrolizumab	80	6 (7.5)	Not reached (-, -)	95.0 (87.1, 98.1)	0.31 (0.12, 0.79)
	Placebo	80	18 (22.5)	Not reached (-, -)	91.2 (82.5, 95.7)	
Stage IIIB	Pembrolizumab	237	60 (25.3)	Not reached (-, -)	83.6 (78.2, 87.8)	0.56 (0.41, 0.78)
	Placebo	230	96 (41.7)	20.4 (15.6, -)	74.8 (68.6, 80.0)	
Stage IIIC	Pembrolizumab	197	69 (35.0)	Not reached (-, -)	75.3 (68.6, 80.8)	0.61 (0.45, 0.82)
	Placebo	195	102 (52.3)	12.9 (8.5, 18.2)	64.3 (57.1, 70.6)	
AJCC 8th edition						
Stage IIIA >1 mm	Pembrolizumab	42	3 (7.1)	Not reached (-, -)	92.7 (79.1, 97.6)	0.76 (0.17, 3.39)
	Placebo	40	4 (10.0)	Not reached (-, -)	95.0 (81.5, 98.7)	
Stage IIIB	Pembrolizumab	164	39 (23.8)	Not reached (-, -)	85.1 (78.5, 89.7)	0.60 (0.41, 0.89)
	Placebo	191	71 (37.2)	Not reached (20.4, -)	79.8 (73.3, 84.9)	
Stage IIIC	Pembrolizumab	267	75 (28.1)	Not reached (-, -)	81.9 (76.7, 86.0)	0.48 (0.36, 0.65)
	Placebo	236	119 (50.4)	15.0 (11.0, 19.4)	67.4 (60.9, 73.0)	
Stage IIID	Pembrolizumab	19	10 (52.6)	12.9 (2.7, -)	57.9 (33.2, 76.3)	0.62 (0.28, 1.37)
	Placebo	20	15 (75.0)	4.9 (2.7, 15.4)	45.0 (23.1, 64.7)	
Pooled Stages IIIC and IIID	Pembrolizumab	286	85 (NR)	NR	NR	0.50 (0.37, 0.66)
	Placebo	256	134 (NR)	NR	NR	
Pooled Stages IIIB, IIIC and IIID	Pembrolizumab	267	75 (NR)	NR	NR	0.53 (0.42, 0.67)
	Placebo	236	119 (NR)	NR	NR	

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; NR = not reported; RFS = recurrence free survival

^a From the product-limit (Kaplan-Meier) method for censored data

^b Pembrolizumab vs placebo. Treatment as covariate stratified by stage. Hazard ratio <1 favour pembrolizumab. Statistically significant results in bold

Source: Tables 2.6-1 to 2.6-7, pp.89-92 and Figure 2.6-3, p.93 of the resubmission

6.20 The relative effect of pembrolizumab versus placebo was similar between disease stage subgroups, with no evidence of a treatment effect interaction by Stage III subgroup (p-value 0.774). Recurrence free survival rates at six months declined as

disease stage progressed (placebo Stage IIIA > 1 mm 95.0% - Stage IIID 45.0%), suggesting pembrolizumab versus placebo is associated with an increasing absolute risk reduction for recurrence with increasing severity of disease.

Subgroup analyses by BRAF status

6.21 Results for recurrence free survival by BRAF status, which was a pre-specified subgroup analysis of the KN054 trial, are presented below. The Clinical Study Report stated that improved recurrence free survival was observed in patients who received pembrolizumab regardless of BRAF mutation status.

Table 8: RFS results by BRAF mutation status

	N	Events (%)	Median RFS (95% CI)	HR (95% CI)
BRAF wildtype				
Pembrolizumab	233	69 (29.6%)	NR (-, -)	0.64 (0.47, 0.87)
Placebo	214	97 (45.3%)	17.1 (13.0, -)	
BRAF mutant				
Pembrolizumab	245	61 (24.9%)	NR (-, -)	0.49 (0.36, 0.67)
Placebo	262	115 (43.9%)	20.4 (14.7, -)	
BRAF mutation status unknown				
Pembrolizumab	36	5 (13.9%)	NR (-, -)	0.95 (0.24, 3.64)
Placebo	29	4 (13.8%)	NR (-, -)	

CI = confidence interval; HR = hazard ratio; NR = not reported; RFS = recurrence free survival
Source: Table 14.2-23, p49; Table 14.2-24, p51; and Table 14.2-25, p53 of KN054 CSR

Table 9: RFS survival rates by BRAF mutation status

	Survival rate, % (95% CI)	
	Mutant	Wildtype
Pembrolizumab	N = 245	N = 233
6 month	82.5% (77.1, 86.8)	80.4% (74.6, 85.0)
12 month	76.1% (70.1, 81.0)	73.0% (66.7, 78.3)
18 month	73.7% (67.2, 79.1)	66.7% (59.3, 73.0)
Placebo	N = 262	N = 214
6 month	72.7% (66.8, 77.7)	71.9% (65.3, 77.5)
12 month	59.2% (52.9, 65.0)	59.7% (52.7, 66.0)
18 month	53.5% (46.3, 60.2)	48.8% (40.4, 56.7)

CI = confidence interval; RFS = recurrence free survival
Source: Tables 4.3-4 and 4.3-5, p132 of Att 6 to the resubmission

Indirect comparison

6.22 The resubmission presented an indirect comparison of recurrence free survival between pembrolizumab (KN054 BRAF mutation subgroups) and supplementary near market comparator dabrafenib+trametinib (COMBI-AD; placebo as common reference), updated with four year follow up data from the COMBI-AD study.

Table 10: Results of the indirect comparison between pembrolizumab and dabrafenib+trametinib

	BRAF status	HR, RFS (95% CI)	Trials involved
Direct: PEMBRO vs. PBO	BRAF MT and WT	0.49 (0.36, 0.67)	KN054
Direct: DAB+TRAM vs. PBO	BRAF MT	0.49 (0.40, 0.59)	COMBI-AD
Indirect: PEMBRO vs. DAB+TRAM	-	1.00 (0.69, 1.44); p = 1.0000	KN054 vs. COMBI-AD [Placebo]

CI = confidence interval; DAB+TRAM = dabrafenib+trametinib; HR = hazard ratio; MT = mutant; PBO = placebo; PEMBRO = pembrolizumab; RFS = recurrence-free survival; WT = wildtype

Source: Table 10, p16 of Attachment 2 of the resubmission.

- 6.23 The resubmission maintained that the results of the indirect comparison demonstrated a similar treatment effect for pembrolizumab compared to dabrafenib+trametinib in the BRAF mutation population receiving adjuvant therapy for Stage III malignant melanoma. The evaluation noted that there was uncertainty associated with the indirect comparison, given potential confounding due to differences in baseline characteristics between treatment arms in the KN054 BRAF mutation status subgroups (PD-1 status and Stage IIIC ≥ 4 nodes) and poor transitivity between studies in terms of maturity of data, and duration of follow up. The PSCR stated that these differences were not clinically meaningful in terms of interpretation of the results. Specifically, that the variation in baseline BRAF status had very little to no impact on the recurrence free survival results. In addition, the PSCR noted that while follow-up duration was different across the trials, the maximum treatment duration of 12 months was consistent, and that event rates in the placebo arms of KN054 and COMBI-AD trials significantly overlapped, further demonstrating exchangeability.
- 6.24 The resubmission argued that the naïve comparison between pembrolizumab and supplementary near market comparator nivolumab, based on the KN054 (pembrolizumab versus placebo) and CA238 (nivolumab versus ipilimumab) trials, suggested pembrolizumab is comparable to nivolumab in terms of recurrence free survival.
- 6.25 The results of a two-step indirect comparison of pembrolizumab versus nivolumab for recurrence free survival, conducted during the November 2018 evaluation using ipilimumab versus placebo (Trial CA029) as a common reference suggested no statistically significant difference between pembrolizumab and nivolumab (HR = 1.17, 95% CI: 0.78, 1.75). However, the evaluation considered that there was considerable uncertainty in the indirect comparison, given the two-step design of the comparison and poor transitivity between Trial KN054, CA238 and CA029 in terms of maturity of data, duration of follow up, AJCC Staging system, inclusion of Stage III and IV populations, and baseline patient characteristics.

Comparative harms

6.26 Key adverse events reported in the KN054 trial are summarised in Table 11 below.

Table 11: Summary of key adverse events in Trial KN054 (AJCC 7th edition; as treated population)

	Pembrolizumab N=509	Placebo N=502	Risk difference (95% CI)	Relative risk (95% CI)
Any adverse events, n (%)				
Any grade	475 (93.3%)	453 (90.2%)	0.03 (0.00, 0.06)	1.03 (1.00, 1.07)
Grade 3-5	158 (31.0%)	96 (19.1%)	0.12 (0.07, 0.17)	1.62 (1.30, 2.03)
Treatment related adverse events, n (%)				
Any grade	396 (77.8%)	332 (66.1%)	0.12 (0.06, 0.17)	1.18 (1.09, 1.27)
Grade 3-5	74 (14.5%)	17 (3.4%)	0.11 (0.08, 0.15)	4.29 (2.57, 7.17)
Grade 3-5 AEOSI	36 (7.1%)	3 (0.6%)	0.06 (0.04, 0.09)	11.83 (3.67, 38.18)
Adverse event discontinuations	62 (12.2%)	8 (1.6%)	0.11 (0.08, 0.14)	7.64 (3.70, 15.8)
Death	1 (0.2%)	0	0.00 (0.00, 0.01)	2.96 (0.1, 72.5)
Most frequent treatment related adverse events of any grade (≥ 5% of patients in either arm)				
Fatigue	143 (28.1%)	135 (26.9%)	0.01 (-0.04, 0.07)	1.04 (0.86, 1.28)
Diarrhoea	94 (18.5%)	82 (16.3%)	0.02 (-0.03, 0.07)	1.13 (0.86, 1.48)
Pruritus	85 (16.7%)	49 (9.8%)	0.07 (0.03, 0.11)	1.71 (1.23, 2.38)
Hypothyroidism	73 (14.3%)	13 (2.6%)	0.12 (0.08, 0.15)	5.54 (3.11, 9.86)
Nausea	58 (11.4%)	43 (8.6%)	0.03 (-0.01, 0.07)	1.33 (0.91, 1.93)
Arthralgia	51 (10.0%)	47 (9.4%)	0.01 (-0.03, 0.04)	1.07 (0.73, 1.56)
Hyperthyroidism	49 (9.6%)	4 (0.8%)	0.09 (0.06, 0.12)	12.1 (4.39, 33.2)
Rash	49 (9.6%)	32 (6.4%)	0.03 (-0.00, 0.07)	1.51 (0.98, 2.32)
Asthenia	48 (9.4%)	34 (6.8%)	0.03 (-0.01, 0.06)	1.39 (0.91, 2.12)
Headache	37 (7.3%)	33 (6.6%)	0.01 (-0.02, 0.04)	1.11 (0.70, 1.74)
Dyspnoea	27 (5.3%)	14 (2.8%)	0.03 (0.00, 0.05)	1.90 (1.01, 3.58)
ALT increased	26 (5.1%)	16 (3.2%)	0.02 (-0.01, 0.04)	1.60 (0.87, 2.95)
Myalgia	26 (5.1%)	15 (3.0%)	0.02 (-0.00, 0.05)	1.71 (0.92, 3.19)

AJCC = American Joint Committee on Cancer; ALT = alanine aminotransferase; AEOSI = adverse event of special interest

Source: Tables 2.5-5 and 2.5-6, pp.84-86 of the resubmission

6.27 No new adverse event data were presented in the resubmission. Larger proportions of patients treated with pembrolizumab experienced any adverse events, treatment related adverse events and grade 3-5 adverse events compared to patients receiving placebo. A larger proportion of patients treated with pembrolizumab discontinued participation due to adverse events.

6.28 The most frequent treatment related adverse events reported by patients treated with pembrolizumab were fatigue (28.1%), diarrhoea (18.5%), pruritus (16.7%), hypothyroidism (14.3%), nausea (11.4%) and arthralgia (10.0%).

6.29 Overall, adverse events reported in Trial KN054 were consistent with the immune mediated events (pneumonitis, colitis, hepatitis, nephritis) and immune mediated endocrinopathies (hyperthyroidism, hypothyroidism, hypophysitis, type 1 diabetes) reported in other pembrolizumab trials for different indications. No new safety signals were identified.

- 6.30 No new data were available to inform the indirect comparisons of safety outcomes for pembrolizumab versus its near market comparators nivolumab and dabrafenib+trametinib.
- 6.31 The resubmission argued that the adverse event profiles for pembrolizumab and nivolumab do not appear to be different across multiple tumours and maintained that in terms of adverse events, pembrolizumab is no worse than nivolumab in patients receiving these treatments as adjuvant therapy for resected Stage III melanoma.
- 6.32 For the indirect comparison of pembrolizumab versus dabrafenib+trametinib, the results of any adverse events, Grade 3-5 (or Grade 3-4) adverse events and discontinuation due to AEs consistently favoured pembrolizumab compared with dabrafenib+trametinib.

Benefits/harms

- 6.33 A summary of the comparative benefits and harms for pembrolizumab versus placebo is presented in the table below.

Table 12: Summary of comparative benefits and harms for pembrolizumab and placebo

Benefits						
Trial KN054 ^a Recurrence free survival (median duration of follow-up 16 months)						
	PEMBRO, n/N (%)	Placebo, n/N (%)	Absolute difference	Hazard ratio (98.4% CI)		
Recurrence or death events, n/N (%)	135/514 (26.3%)	216/505 (42.8%)	-	-		
Median RFS, months	7th edition 8th edition	Not reached	20.4 (16.2, -)	-	0.57 (0.43, 0.74) 0.55 (0.42, 0.71)	
No recurrence at 6 months, % (95% CI)	82.2% (78.6, 85.3)	73.3% (69.2, 77.0)	8.9%	-		
No recurrence at 12 months, % (95% CI)	75.4% (71.3, 78.9)	61.0% (56.5, 65.1)	14.4%	-		
No recurrence at 18 months, % (95% CI)	71.4% (66.8, 75.4)	53.2% (47.9, 58.2)	18.2%	-		
Harms						
	PEMBRO, n/N	Placebo, n/N	Relative risk (95% CI)	Event rate/100 patients		Risk difference (95% CI)
				PEMBRO	Placebo	
Grade 3-5 AEs	158/509	96/502	1.62 (1.30, 2.03)	31.0	19.1	0.12 (0.07, 0.17)
Treatment related AEs leading to discontinuation	62/509	8/502	7.64 (3.70, 15.8)	12.2	1.6	0.11 (0.08, 0.14)
Treatment-related Grade 3-5 AEOI	36/509	3/502	11.83 (3.67, 38.18)	7.1	0.6	0.06 (0.04, 0.09)

AE = adverse event; AEOI = adverse event of special interest; CI = confidence interval; PEMBRO = pembrolizumab; RFS = recurrence free survival

^a Based on AJCC 7th edition staging system unless otherwise noted. Statistically significant results in bold

Source: Tables 2.5-5 and 2.5-6, pp.84-86 of the resubmission

- 6.34 The assessment of benefits and harms for patients with Stage III malignant melanoma (KN054, ITT population) has been updated from the November 2018 submission, including AJCC 8th edition subgroups.
- 6.35 On the basis of evidence presented in the resubmission for Trial KN054, for every 100 patients treated with pembrolizumab in comparison to placebo:

- Approximately 18 fewer patients would experience recurrence, based on Kaplan-Meier event rates at 18 months;
 - Approximately 12 additional patients would experience a Grade 3-5 all-cause AE based on a median duration of follow-up of 16 months;
 - Approximately 11 additional patients would experience a treatment related AE leading to discontinuation based on a median duration of follow-up of 16 months;
 - Approximately 6 additional patients would experience a treatment related Grade 3-5 adverse events of special interest based on a median duration of follow-up of 16 months.
- 6.36 On the basis of *post hoc* subgroup analyses of Trial KN054 by AJCC 8th edition staging system Stage III subgroups, for every 100 patients treated with pembrolizumab in comparison to placebo (estimates calculated by applying the hazard ratio from the ITT population to the Kaplan-Meier event rates at 6 months reported in the placebo arm of each subgroup):
- Approximately 2 fewer patients with Stage IIIA disease would experience recurrence;
 - Approximately 9 fewer patients with Stage IIIB disease would experience recurrence;
 - Approximately 15 fewer patients with Stage IIIC disease would experience recurrence; and
 - Approximately 25 fewer patients with Stage IIID disease would experience recurrence.

Clinical claim

- 6.37 The resubmission described pembrolizumab as superior in terms of effectiveness with inferior, but manageable, safety compared to current standard of care (observation/placebo). The ESC and PBAC considered that the claim of superior efficacy presented in the resubmission was reasonable in terms of recurrence free survival; however the magnitude of any benefit remained uncertain. The ESC and PBAC considered that the claim of inferior safety was reasonable and adequately supported by the data.
- 6.38 Based on the indirect comparisons between pembrolizumab and the near market comparators as adjuvant therapy for patients with completely resected Stage III malignant melanoma, the resubmission claimed that pembrolizumab is no worse in terms of efficacy and safety compared to nivolumab and no worse in terms of efficacy compared to dabrafenib+trametinib, with a more favourable safety profile.

Economic analysis

- 6.39 The resubmission presented a modelled economic evaluation of adjuvant treatment with pembrolizumab for patients with Stage III resected melanoma compared to no active treatment (watchful waiting) based on the KN054 trial. KN054 provided a direct comparison of pembrolizumab versus placebo for transitions commencing in the recurrence free survival health state; data from external sources was used to model transitions from the locoregional and distant metastases health states and overall survival. The type of economic evaluation presented was a cost utility analysis.
- 6.40 Compared with the previous submission, the resubmission included additional analyses by Stage III melanoma substage according to the AJCC 8th edition staging system; new analyses comparing modelled outcomes with comparable published outcomes; and substates within the distant metastases health state to explore the impact of eligibility for treatments for advanced melanoma in the pembrolizumab treatment arm.

Table 13: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	Life years; quality-adjusted life years
Time horizon	10 years (up to lifetime in sensitivity analysis)
Methods used to generate results	Markov cohort expected value analysis (with half-cycle correction)
Treatments	Pembrolizumab, watchful waiting
Health states	Four health states: recurrence-free; locoregional recurrence; distant metastases; death
Cycle length	Weekly
Transition probability	Transition probabilities were derived through primary analyses of patient-level data from the KN054 trial and a targeted literature search for relevant clinical inputs not estimable using trial data. Transitions between health states were informed by parametric functions fitted to observed data (trial data not used in the model)
Discount rate	5% for costs and outcomes
Software package	Excel 2016

Source: Table 3.1-1, p.120 of the resubmission

- 6.41 All patients start in the recurrence-free health state, following resection of their melanoma. During each weekly cycle, patients could remain recurrence-free, experience locoregional recurrence, distant metastases, or die. Patients in the recurrent health states (locoregional recurrence and distant metastases) accrued higher costs and lower utilities than patients who remained recurrence free.
- 6.42 Key drivers of the economic model are summarised in the table below.

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Table 14: Key drivers of the model

Description	Method/Value	Impact
Transitions from the recurrence free health state	Transitions from the recurrence free health states were informed by a parametric multistate modelling approach fitted to data from KN054. In the base case, separate parametric models were fitted for each treatment arm of KN054 to inform the transition probabilities. Trial data were not directly included in the model base case. The ESC again considered that given the short duration of follow up in KN054 (median follow up of 16 months), extrapolations based on these data were highly uncertain. Overall, transition probabilities and extrapolation from the recurrence free health state had a large impact on the economic model.	High, favours pembrolizumab
Transitions from the distant metastases health state	The ESC again noted that transitions from distant metastases to death were not informed by trial data, rather they were informed by published overall survival and RFS results for pembrolizumab 2 mg/kg in advanced melanoma (Trial KN006), and a network meta-analysis comparing treatments for advanced melanoma in terms of overall survival and PFS, neither of which were representative of the modelled population. The ESC noted that there was no reliable evidence to determine the extent to which adjuvant treatment of Stage III melanoma with pembrolizumab delivers an overall survival benefit. The ESC also considered that the use of external evidence data introduced substantial uncertainty.	High, favours pembrolizumab
Treatment effect maintained over the duration of the model	The model assumed an ongoing treatment effect of adjuvant pembrolizumab over the duration of the model. Only limited trial data were available to inform the model and extrapolation beyond this period was uncertain. The ESC considered that the duration of treatment effect relating to adjuvant treatment of Stage III melanoma with pembrolizumab was highly uncertain. The continued treatment effect in terms of recurrence free survival for the model duration provided a large incremental gain in recurrence free survival in the pembrolizumab arm, compared with the watchful waiting arm. The structure of the model did not allow sensitivity analyses to adequately quantify the uncertainty associated with the extrapolation of treatment effect over the 10 year duration of the model.	High, favours pembrolizumab
Cost of treatments for advanced melanoma	The cost of subsequent therapies, plus disease management costs, in the advanced setting for unresectable melanoma (approximately \$██████ per patient) contributed substantially to the cost offsets, reducing the total incremental costs of pembrolizumab over watchful waiting. The proportion of the patients who progress to the distant metastases health state where costs of advanced treatment are applied in each arm was uncertain as it was based on immature recurrence free survival data. The ESC noted that the cost offsets were high and that removing them from the analysis resulted in the ICER increasing by more than double.	High, favours pembrolizumab

PFS = progression free survival

Source: compiled during the evaluation using information in Section 3 of the resubmission

6.43 In the model base case, separate parametric models were fitted for each treatment arm to inform transition probabilities, rather than applying hazard ratios to the watchful waiting arm to inform the pembrolizumab arm. This approach was not justified in the resubmission.

6.44 Transition probabilities from the recurrence free health state were unchanged compared with the previous submission. To fit parametric models to each of the individual health state transitions, standard survival-analysis methods were applied to each cause-specific event with one modification to account for competing risks. When analysing time to each specific type of recurrence-free survival failure, the two competing failure types were treated as censoring events. It was unclear if the

resubmission used an appropriate model for competing risks analysis. Censoring competing events will bias standard survival analysis (such as the Kaplan-Meier method which assumes that censoring is non-informative and independent of the outcome of interest). Therefore, merely censoring other events violated both of these assumptions (as competing events are known, and unlikely to be independent) and was not an appropriate adjustment for competing risks. Censoring competing events was likely to overestimate the probability of the event of interest and would provide misleading results. The NICE Decision Support Unit Technical Support Document 19 (Partitioned survival analysis for decision modelling in health care) recommends analysis in the presence of competing risks be conducted using cumulative incidence curves. The PSCR agreed that treating competing failure types as censoring events might overestimated the probabilities of each individual transition, but that this was addressed in the model as the probability of each transition starting from the recurrence free state depended on all three cause-specific hazards functions. Occurrence of individual events may still be overestimated in the model.

- 6.45 Large proportions of patients in the watchful waiting arm enter the distant metastases health state, where most of the costs and disutility weights were applied. After 5 years, 55.7% of patients in the pembrolizumab arm were alive without distant metastases, compared with 30.2% in the watchful waiting arm. At 10 years, this was 42.4% and 16.7% respectively. This did not align with published survival estimates (see Table 15).
- 6.46 Transition probabilities from the locoregional recurrence and distant metastases health states were unchanged compared with the previous submission. The ESC remained concerned that the trial data were immature. The PBAC considered that as overall survival data were not yet available from the KN054 trial, there was no reliable evidence to determine the extent to which adjuvant treatment of Stage III melanoma with pembrolizumab delivered an overall survival benefit.
- 6.47 The hazard ratios generated in the network meta-analysis and used to inform transitions from distant metastases to death were based on studies of patients who did not receive adjuvant therapy with a PD-1 or PD-L1 inhibitor. Furthermore, the resubmission did not assess the transitivity of the trials in the network meta-analysis. Transitions from the distant metastases health state were therefore highly uncertain. The model was sensitive to costs of therapies for advanced melanoma.
- 6.48 The distant metastases health state included new modelled substates according to the patient's eligibility for treatment in the advanced setting in the pembrolizumab treatment arm: rechallenge-eligible (can receive pembrolizumab in the advanced setting, subject to specific criteria for retreatment); immunotherapy-eligible (no restriction on receiving treatment in the advanced setting) or immunotherapy-ineligible (cannot receive pembrolizumab or nivolumab in the advanced setting). In the watchful waiting arm, all patients received treatment according to the immunotherapy-eligible mix. In the base case, it was assumed that for the

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pembrolizumab arm patients would receive no further treatment with pembrolizumab (i.e. for advanced melanoma) unless they transition from recurrence-free to distant metastases at least 18 months after adjuvant treatment initiation. Given the current data cut off (median 16 months follow up) the proportion who become eligible for retreatment is unknown.

- 6.49 The resubmission included a comparison of modelled outcomes for overall survival in the watchful waiting arm with published estimates. Although there are limitations associated with comparing across different patient cohorts, and in comparing overall survival to melanoma-specific survival, the AJCC publications provide some of the most recent estimates of melanoma specific survival by melanoma substage. The resubmission also included a comparison against an Australian natural history publication (Haydu 2017). The results of the comparison of modelled overall survival with published survival rates are summarised in Table 12.

Table 15: Comparison between modelled overall survival and published overall survival rates

Melanoma stage	Modelled overall survival (watchful waiting arm)	AJCC 8 th edition (Gershenwald 2017; 2018)	Haydu (2017)
5 year survival			
All Stage III	55.4%	77%	NA
Stage IIIA	87.7%	93%	81.4%
Stage IIIB	56.4%	83%	64.0%
Stage IIIC	47.9%	69%	44.5%
Stage IIID	38.8%	32%	9.8%
10 year survival			
All Stage III	26.6%	69%	NA
Stage IIIA	63.5%	88%	
Stage IIIB	26.4%	77%	
Stage IIIC	17.3%	60%	
Stage IIID	11.1%	24%	

Source: Table 3.7-3, p.184 of the resubmission

- 6.50 The ESC were concerned that the modelled estimates of overall survival were low. Overall survival estimates for all Stage III patients in the watchful waiting arm of the model (55.4% at five years and 26.4% at 10 years) appeared to be underestimated when compared to melanoma specific survival probabilities presented in the AJCC 8th edition staging system (77% at five years, 69% at 10 years). In addition, the ESC considered that projected overall survival from the AJCC 8th edition and Haydu et al. (2017) may still underestimate overall survival for the watchful waiting arm of the economic model, as they include both resected and unresected patients, do not reflect recent improvements in surgery, sentinel lymph node biopsy, and imaging, and do not reflect the widespread use of systemic therapies in advanced disease. The PSCR and pre-PABC response maintained that the modelled outcomes were comparable with published estimates, primarily the adjuvant ipilimumab trial (Eggermont, 2015). The ESC noted that the survival estimates in both treatment arms remained poor in comparison with most recent estimates from the International Melanoma database,

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which informs the AJCC 8th edition melanoma staging system, and considered that the modelled outputs in terms of overall survival were not only likely underestimated, but clinically implausible. The ESC also noted that the structure of the economic model did not allow for this uncertainty to be tested in sensitivity analyses.

- 6.51 The base case utilities were unchanged from the November 2018 submission. The utilities used did not have a large impact on the economic model.
- 6.52 The base case results of the economic model are summarised below. The PSCR included a revised ICER, which modelled the impact of improved survival for patients with advanced melanoma. The PSCR decreased the exponential rate of transition for pembrolizumab by altering the rate at which patients transition from the distant metastases state to death, resulting in a 5-year overall survival rate of 77% for the watchful waiting arm to align with the AJCC 8th edition results.

Table 16: Results of the economic evaluation

Component	Pembrolizumab	Watchful waiting	Increment
July 2019 resubmission			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Life years	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]
Incremental cost/LY gained			\$ [REDACTED]
PSCR to July 2019 resubmission			
Decreasing exponential rate of transition, DM→Death in Pembro arm, incremental cost/QALY gained			\$ [REDACTED]
November 2018 submission			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Life years	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]
Incremental cost/LY gained			\$ [REDACTED]

DM = distant metastases; LY = life year; pembro = pembrolizumab; QALY = quality-adjusted life year

Source: Table 3.8-5, p.178 of the resubmission; Att 18 CEMs.xls; November 2018 pembrolizumab commentary; and p3 of the PSCR

- 6.53 Based on the economic model, adjuvant treatment with pembrolizumab (effective price) for Stage III resected melanoma was associated with a cost per QALY gained of \$15,000/QALY - \$45,000/QALY and a cost per life year gained of \$15,000/QALY - \$45,000/QALY compared with watchful waiting. The ICERs in the resubmission were similar to those in the November 2018 submission consistent with there being few changes made to the economic model.
- 6.54 QALY gains in the pembrolizumab treatment arm primarily accrued in the recurrence free health state. The QALY gain estimate for pembrolizumab versus watchful waiting was 1.03 QALYs. Only 0.03 QALYs (3% of the total QALY gain) were accrued during the first 16 months of the model time horizon, the median period for which follow up data from the KN054 trial were available, with the remaining 97% of the QALY gain accrued during the modelled period. The ESC considered that the QALY gain accrued during the modelled period was substantially overestimated in favour of pembrolizumab.

- 6.55 The difference in total cost between the treatment arms was primarily driven by cost of adjuvant pembrolizumab (\$██████), which was offset by a reduction in cost of subsequent treatment of advanced melanoma (\$██████), and disease management costs (\$██████). The ESC considered that the cost-offsets were overestimated.
- 6.56 The ESC noted that a number of the issues described in consideration of the economic model in November 2018 remained, and therefore considered that economic model continued to be unreliable and lacking in face validity, and that the ICERs were likely underestimated as a number of assumptions were favourable to pembrolizumab. The pre-PBAC response stated that significant changes were made to the economic model, including additional analyses by Stage III substage, new analyses comparing modelled outcomes with comparable published outcomes and substates within the distant metastases health state to explore the impact of eligibility for treatments for advance melanoma in the pembrolizumab treatment arm. The PBAC noted the similar results for the November 2018 and current models, and overall did not consider the model changes to be significant.
- 6.57 Stage III disease is associated with heterogeneous outcomes; five-year melanoma-specific survival rates range from 93% for Stage IIIA disease to 32% for Stage IIID disease (8th edition). The model therefore included modelled outcomes by Stage III melanoma subgroup (see table below). It should be noted that the distribution of patients across the melanoma substages in clinical practice may be different to that in Trial KN054. The PSCR presented an additional ICER to align with the proposed change to the PBS indication of 'Resected Stage IIIB, IIIC or IIID malignant melanoma' based on the weighted proportion of patients in each substage in KN054.
- 6.58 The ESC considered that the combined ICER presented in the PSCR for patients with Stage IIIB, IIIC and IIID was unreliable as the ICERs for each of the individual subgroups were unreliable. The ESC considered that a more reliable approach would be to use the hazard ratio derived from the whole trial population and to apply this to the baseline risk in the watchful waiting arm for the subgroup of interest (given the absence of treatment effect modification by subgroup). The pre-PBAC response stated that this approach was not used as a proportional hazards relationship had not been established and, consistent with previous work in immunotherapy treatment of cancers, was unlikely to apply.

Table 17: Results of the economic evaluation for patients by melanoma substage

Component	Pembrolizumab	Watchful waiting	Increment
Stage IIIA			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Life years	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]
Incremental cost/LY gained			\$ [REDACTED]
Stage IIIB			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Life years	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]
Incremental cost/LY gained			\$ [REDACTED]
Stage IIIC			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Life years	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]
Incremental cost/LY gained			\$ [REDACTED]
Stage IIID			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Life years	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/QALY gained			\$ [REDACTED]
Incremental cost/LY gained			\$ [REDACTED]
PSCR			
Stage IIIB, IIIC and IIID population, incremental cost/QALY gained - Weighted			\$ [REDACTED]

LY = life year; PSCR = pre-Sub-Committee response; QALY = quality-adjusted life year
 Source: Section 3.9 of the resubmission; Att 18 CEMs.xls and Table 2, p5 of the PSCR

- 6.59 The ICER for Stage IIIA >1 mm was \$105,000/QALY - \$200,000/QALY . This result is likely driven by reduced risk of disease recurrence in this population, which was evident in the low number of events in the KN054 trial. The ICER for Stage IIID (\$15,000/QALY - \$45,000/QALY) was also higher than for Stage IIIB or IIIC (less than \$15,000/QALY and less than \$15,000/QALY respectively), which appeared inconsistent given higher risk of recurrence and poorer prognosis associated with Stage IIID melanoma (larger relative treatment effect expected). This result was likely driven by low patient numbers (3.9% of trial population) and data sparseness (low numbers of events) in the Stage IIID population in the KN054 trial. The ESC noted that the trial was not powered for the subgroup analyses that inform the economic model, and therefore the highly uncertain results should be interpreted with caution.
- 6.60 The table below summarises the results of key sensitivity analyses presented in the resubmission and additional sensitivity analyses conducted during the evaluation.

Table 18: Sensitivity analyses

Input values	ICER vs. comparator (\$/QALY)
Base case	\$ [REDACTED]
Time horizon (base case = 10 years)	
7 years	\$ [REDACTED]
10 years	\$ [REDACTED]
Efficacy and transition probabilities	
Distribution used for RF→LR and RF→DM: Exponential	\$ [REDACTED]
Distribution used for RF→LR and RF→DM: Gompertz	\$ [REDACTED]
Transitions from RF: parametric models with a time-constant treatment effect	\$ [REDACTED]
Subsequent therapies for advanced melanoma	
Include costs of first-line advanced regimens only	\$ [REDACTED]
Assume same mix of advanced treatments following adjuvant pembrolizumab and watchful waiting	\$ [REDACTED]
Costs of advanced treatment removed	\$ [REDACTED]
Convergence of treatment effect	
Assuming linear convergence between pembrolizumab and watchful waiting (for RFS, locoregional recurrence, distant metastases and death) between year 5 and year 10	\$ [REDACTED]

DM = distant metastases; LR = locoregional recurrence; OS = overall survival; QALY = quality adjusted life year; RF = recurrence free; RFS = recurrence free survival

Source: Table 3.10-1, pp.202-203 of the resubmission; additional sensitivity analyses conducted during the evaluation based on Att 18 CEMs Excel spreadsheet

The redacted table shows ICERS in the range of \$15,000/QALY - \$75,000/QALY.

6.61 The results of the sensitivity analysis showed that the model was sensitive to the parametric function used to model the treatment effect, time horizon and convergence of treatment effect between year 5 and year 10. The pre-PBAC response stated that the ICER calculated through convergence of treatment effect was unable to be verified and considered that convergence may have been applied to the composite outcome rather than the substates, which have different costs and outcomes.

6.62 The ESC noted that the structure of the economic model did not allow sensitivity analyses to adequately quantify the uncertainty associated with the extrapolation of the treatment effect over the time horizon of the model. This is important given the immaturity of the recurrence free survival data (median recurrence free survival not yet reached in the pembrolizumab arm), the lack of overall survival data from KN054, and the poor face validity of the model (i.e. did not model reasonable survival estimates in the watchful waiting arm).

Drug cost/patient/course

6.63 The resubmission applied an average relative dose intensity of 99.7% to the drug acquisition cost per infusion in the base case of the economic model, but not to the

financial estimates, resulting in a small difference in the total cost per patient per course.

Table 19: Drug cost per patient for pembrolizumab for the adjuvant treatment of resected Stage III melanoma

	Trial dose and duration	Model	Financial estimates
Mean dose	200 mg every 3 weeks	200 mg every 3 weeks	200 mg every 3 weeks
Mean duration	█ cycles (█ weeks) ^a	█ cycles (█ weeks) ^a	█ cycles (█ weeks) ^a
Relative dose intensity	99.7% ^b	99.7% ^b	Not applied
Cost/patient/cycle (3 weeks)	\$█	\$█	\$█
Cost/patient/course	\$█	\$█	\$█

Source: Att 20 BIM.xlsx Section 4 spreadsheet; Att18 CEM.xlsm Section 3 spreadsheet; Section 2.4.2, pp66-67 of the resubmission.

^a From trial-based progression-free survival curves, average treatment duration for Stage IIIA, B, C and D. One cycle is 3 weeks duration.

^b Trial-based relative dose intensity. The resubmission reported that the relative dose intensity was not included in the modelled financial estimates (Table 1.1-1, p3 of the resubmission), however the resubmission later stated that the trial-based relative dose intensity was applied to the drug acquisition cost per infusion in the base case of the model in the adjuvant setting (Section 3.6.1.1, p158 of the resubmission).

^c Weighted average (36.1% public/63.9% private hospital use) dispensed cost per administration (2 x 100 mg vials) x relative dose intensity; effective price.

^d Weighted average (36.1% public/63.9% private hospital use) dispensed cost per administration (2 x 100 mg vials); effective price. Dispensed cost per administration for 2 x 100 mg vials is \$█ for public hospital; \$█ for private hospital (effective prices)

^e Weighted average cost/cycle x relative dose intensity x mean duration; effective price.

^f Weighted average cost/cycle x mean duration; effective price.

6.64 The estimated (effective) drug cost per patient per course in the previous submission was \$█.

Estimated PBS usage & financial implications

6.65 The resubmission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the utilisation and financial implications associated with PBS listing of pembrolizumab for the adjuvant treatment of resected Stage III melanoma, excluding Stage IIIA ≤ 1mm metastases.

6.66 Compared with the previous submission, the ESC noted that patient numbers were slightly increased despite the PBAC considering that the utilisation estimates were overestimated in November 2018 (paragraph 7.11, pembrolizumab PSD, November 2018). The resubmission used an updated data source (AIHW/NSW Cancer Institute, 2010) to estimate the incident population (8.5% compared with 8% previously) which the ESC noted was likely high when compared to more recent figures released by the National Cancer Control Indicators (26 April 2018) which stated 3.0% of patients were Stage III at diagnosis. The resubmission estimated the number of patients with Stage III melanoma excluding Stage IIIA ≤ 1 mm in line with the proposed restriction (applying a lower uptake rate [50%] to the predicted proportion of Stage IIIA patients); and estimated cost offsets associated with the avoidance of disease recurrence and treatment of advanced melanoma. Prices were updated to reflect changes to hospital and dispensing fees.

6.67 The pre-PBAC response stated that the National Cancer Control Indicators were derived from 2011 AIHW data, and that recently released data from the NSW Cancer

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Institute (2019) based on diagnosis rates from 2011 to 2015 demonstrate that the regional (Stage III) diagnosis rate is 8.6%.

Table 20: Expected use and financial impact of listing pembrolizumab for the adjuvant treatment of Stage III melanoma (excluding Stage IIIA ≤ 1 mm)

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Patient numbers						
Melanoma annual incidence	14,877	15,205	15,533	15,862	16,190	16,519
Stage III (8.5%)	1,265	1,292	1,320	1,348	1,376	1,404
% of Stage III which is resectable (89%)	1,125	1,150	1,175	1,200	1,225	1,250
% who have progressed from Stage I/II (55%) and which is resectable (89%)	1,376	1,406	1,436	1,467	1,497	1,527
Catch up group (resected in the 13 weeks prior to listing)	275	-	-	-	-	-
Eligible patients for adjuvant treatment	2,776	2,556	2,611	2,667	2,722	2,777
Patients by melanoma stage incorporating uptake rate						
Stage IIIA (8.3% of total, 50% uptake)	116	107	109	111	113	116
Stage IIIB (36.5% of total, 85% uptake)	860	792	809	826	843	861
Stage IIIC (51% of total, 85% uptake)	1204	1109	1133	1157	1181	1205
Stage IIID (4.2% of total, 85% uptake)	98	91	92	94	96	98
Total patient population	2,278	2,099	2,143	2,188	2,233	2,280
Number of pembrolizumab administrations (based on time on treatment curves KEYNOTE-054)						
Stage IIIA (cycles)						
Stage IIIB (cycles)						
Stage IIIC (cycles)						
Stage IIID (cycles)						
Overall (cycles)						
Number of vials of pembrolizumab (2 per administration)						
Overall						
Number of scripts attracting co-payment (2 per patient)						
Overall						
Dispensed cost (effective price: \$ per administration)						
Overall	\$	\$	\$	\$	\$	\$
Patient co-payments (average copayment \$18.51)						
Overall	\$	\$	\$	\$	\$	\$
Effective net price (less patient co-payments)						
Overall	\$	\$	\$	\$	\$	\$
November 2018 submission						
Total patient numbers	2,172	2,001	2,045	2,089	2,133	2,177
Overall cost	\$	\$	\$	\$	\$	\$

Source: Constructed during the evaluation using 'Att 20' BIM Excel spreadsheet provided with the resubmission; November 2018 pembrolizumab commentary

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- 6.68 The net cost to the PBS/RPBS of listing pembrolizumab for the adjuvant treatment of Stage III resected melanoma (excluding Stage IIIA ≤ 1 mm) was estimated to be up to more than \$100 million million in the sixth year of listing (published price more than \$100 million). The estimated cumulative net cost over six years was more than \$100 million (published price more than \$100 million). The net cost to the PBS/RPBS in the November 2018 submission was estimated to be more than \$100 million in the sixth year of listing, and the estimated cumulative net cost over six years was estimated to be more than \$100 million.
- 6.69 The resubmission assumed that the incident population included both patients newly diagnosed with Stage III melanoma, and those initially diagnosed with Stage I or II melanoma who had experienced disease progression. This approach appeared reasonable, but it was difficult to exclude potential double counting. As the publication identifying the number of incident patients was not provided, it was unclear whether there was any overlap between these populations (i.e. incident Stage III may represent those newly diagnosed, or newly diagnosed with Stage III regardless of previous melanoma status).
- 6.70 The resubmission assumed treatment uptake rates of 50% in Stage IIIA disease, in order to account for a smaller proportion of patients in this stage being eligible for or electing adjuvant treatment, and rates of 85% for Stages IIIB-IIID. It is unclear whether these uptake rates would be realised in practice. The PBAC previously considered that an uptake rate of 85% was high (paragraph 6.59, Pembrolizumab minutes, November 2018).
- 6.71 The resubmission included cost offsets for advanced melanoma treatment avoided in the case that pembrolizumab is listed for the adjuvant treatment of resected Stage III melanoma. Extrapolated rates from the economic model were incorporated to determine the number of patients who would be offset from the currently reimbursed unresectable Stage III, or Stage IV setting in any given year following the PBS listing of pembrolizumab in the adjuvant treatment setting. This approach compared the difference in retreatment rates in the world with and without adjuvant pembrolizumab. Because these were based on modelled estimates for progression to distant metastases, which were likely to be overestimated in the model, the cost offsets were likely to be overestimated. As distant metastases-free survival was not assessed at the October 2017 time point of the KN054 trial due to an insufficient number of events, it is unclear how large this population will be in practice.
- 6.72 The net cost to the PBS after cost offsets (due to patients not progressing to distant metastases and therefore not requiring treatment in the unresectable or metastatic setting), is summarised in the table below. The PSCR provided a revised net cost to the PBS, after cost offsets, which excluded all Stage IIIA patients.

Table 21: Net costs to the PBS/RPBS after offsets for advanced melanoma treatment applied

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Stage IIIA	\$	\$	\$	\$	\$	\$
Stage IIIB	\$	\$	\$	\$	\$	\$
Stage IIIC	\$	\$	\$	\$	\$	\$
Stage IIID	\$	\$	\$	\$	\$	\$
Overall	\$	\$	\$	\$	\$	\$
PSCR to the July 2019 resubmission						
Overall	\$	\$	\$	\$	\$	\$

Source: Compiled during the evaluation from information presented in 'Att 20 BIM' Excel spreadsheet; and Table 3, p5 of the PSCR

6.73 The net cost to the PBS/RPBS of listing pembrolizumab for the adjuvant treatment of Stage III resected melanoma (excluding Stage IIIA) after cost offsets were applied was estimated to be more than \$100 million in the sixth year of listing. The estimated cumulative net cost over six years was more than \$100 million.

Quality Use of Medicines

6.74 The resubmission outlined a number of activities to promote the safe and effective use of pembrolizumab, including the development of educational materials, the delivery of education programs, and the provision of a telephone medical information service to respond to questions from patients, carers and health care professionals.

Financial Management – Risk Sharing Arrangements

6.75 The sponsor indicated that they were willing to enter into a Deed of Agreement for supply of pembrolizumab in the adjuvant treatment of Stage III melanoma, including a Special Pricing Arrangement as well as annual subsidisation caps based on appropriate patient numbers.

6.76 The resubmission stated that in order to structure reasonable RSAs that accommodate adjuvant treatment for resected Stage III patients, the existing deed for advanced melanoma patients would also need to be considered due to the interdependence between the two populations. The sponsor would be willing to negotiate an RSA that allows for the treatment of melanoma patients across the adjuvant and metastatic settings based on appropriate patient numbers and associated offsets. The PBAC advised that any RSA should encompass adjuvant and unresectable or metastatic use of the PD-1 inhibitors and consider that any other PD-1s recommended for the treatment of adjuvant melanoma in the future should be included within the same subsidisation caps. The resubmission calculated costs to the PBS taking into account the impact on PD-1 treatment and patient numbers in the unresectable or metastatic setting. The PSCR stated that the current melanoma deed has inappropriately low numbers and that any future RSA would need to take the current melanoma deed into account.

- 6.77 The PBAC advised that any subsidisation caps should include a reduction to the existing caps in the unresectable or metastatic setting to account for patients who no longer required treatment due to adjuvant treatment providing a cure. The PBAC considered that any reduction in use in the unresectable or metastatic setting was unlikely to be observed in the first year of the adjuvant listing.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend listing of pembrolizumab as an adjuvant treatment for completely surgically resected Stage IIIB, IIIC or IIID melanoma. The PBAC acknowledged that there was a high clinical need for effective therapies to reduce the risk of recurrence of resected Stage III melanoma, and considered that in some circumstances recurrence was less likely for those treated with pembrolizumab compared to placebo. However, the PBAC considered that due to the limited duration of follow-up in the key trial, KN054, the magnitude of the clinical benefit was uncertain. The PBAC considered that the modelled incremental benefit, in terms of overall survival, was substantially overestimated and, as a result, the economic model did not provide a reliable basis for assessing the cost-effectiveness of pembrolizumab. The PBAC also remained concerned about the high overall financial opportunity cost.
- 7.2 The PBAC acknowledged the consumer comments, which were supportive of listing and described a range of benefits including improved survival and quality of life, and the strong support from the Medical Oncology Group of Australia.
- 7.3 The PBAC noted that the proposed patient population was updated in the Pre-Sub-Committee Response (PSCR) from patients with completely resected Stage III malignant melanoma and at a high risk of recurrence (defined as Stage IIIA (metastases > 1 mm), IIIB, IIIC or IIID disease based on the 8th edition of the American Joint Committee on Cancer (AJCC) melanoma staging system) to patients with Stage IIIB, IIIC or IIID disease. The PBAC noted that this was consistent with advice provided for the near market comparators (nivolumab and dabrafenib+trametinib) in March 2019.
- 7.4 The PBAC reaffirmed that standard of care (routine follow-up) was the appropriate main comparator for pembrolizumab as adjuvant treatment for melanoma. Nivolumab was also considered for the same indication at the July 2019 meeting and was a near market comparator. Dabrafenib+trametinib was also considered for adjuvant treatment of patients with BRAF mutant melanoma at the July 2019 meeting and was a near market comparator for the BRAF mutant subgroup of patients.
- 7.5 The PBAC noted that the resubmission was again based on trial KN054 comparing pembrolizumab to placebo as adjuvant therapy in patients with completely resected Stage III melanoma. The PBAC noted that no new clinical evidence was presented in the resubmission, but that the resubmission did present new *post hoc* subgroup analyses using the AJCC 8th edition staging system.

- 7.6 The PBAC remained concerned that the data were immature and, that at the median duration of follow-up (16 months), the median recurrence free survival had not been reached for patients in the pembrolizumab arm (interim analysis: HR = 0.57; 95% CI: 0.43, 0.74) and that no overall survival data were available. The PBAC again considered that the claim that pembrolizumab was superior compared to placebo in terms of recurrence free survival was reasonable, but due to the immaturity of the data considered that the magnitude of the treatment effect was highly uncertain.
- 7.7 In terms of overall survival, the PBAC considered that further evidence was required to quantify the relationship between recurrence free and overall survival with PD-1 inhibitor therapy.
- 7.8 The PBAC noted that the resubmission described pembrolizumab as inferior compared to placebo in terms of safety, but that the safety profile was manageable. The PBAC considered that this was reasonable.
- 7.9 The PBAC noted the indirect comparison between pembrolizumab and nivolumab, and for the BRAF mutant population the indirect comparison between pembrolizumab and dabrafenib+trametinib. Acknowledging the indirect nature of the comparisons and the likely transitivity issues between the trials, the PBAC noted that in terms of recurrence free survival, there were no statistically significant differences between pembrolizumab and nivolumab (HR = 1.17; 95% CI: 0.78, 1.75) or pembrolizumab and dabrafenib+trametinib (HR = 1.00; 95% CI: 0.39, 1.44). The PBAC considered the upper 95% confidence limit for the comparison with dabrafenib+trametinib supported non-inferiority. The PBAC noted the upper 95% confidence limit for the comparison versus nivolumab was higher; however, overall considered the claim of non-inferiority was reasonable and consistent with the conclusion for the unresectable or metastatic setting.
- 7.10 The PBAC noted that some minor changes were made to the economic model in response to the November 2018 consideration; however, a number of concerns remained, including:
- Overall survival in both arms of the model, but particularly the placebo arm, was low compared to 10 year survival data presented in the AJCC 8th edition. The PBAC noted the comments provided by the ESC in paragraph 6.50 and agreed that the modelled overall survival estimates were not only underestimated, but clinically implausible;
 - Modelled data were based on immature recurrence free survival data from the KN054 trial; thus, the true magnitude of the treatment effect of pembrolizumab, and whether it would be maintained over time was uncertain. In addition, no overall survival data were available to determine the extent to which adjuvant pembrolizumab delivered an overall survival benefit. The PBAC, noting the use of external evidence to estimate the transition probabilities from distant metastases to death, considered that the incorporation of external data into the model introduced substantial uncertainty;

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- The model relied on the surrogate relationship between recurrence free survival and overall survival which remained uncertain;
 - The relevance of post-recurrence inputs for the adjuvant pembrolizumab arm remained uncertain, given that there were no data for patients who received a PD-1 inhibitor in both the adjuvant and unresectable settings and the proportion of patients likely to become eligible for retreatment is unknown.
- 7.11 The PBAC noted the modelled gain in QALYs for pembrolizumab versus watchful waiting of 1.03 was highly uncertain given only 0.03 QALYs (3% of the total QALY gain) were accrued during the first 16 months of the model time horizon, the median period for which follow up data from the KN054 trial were available, with the remaining 97% of the QALY gain accrued during the modelled period. The PBAC noted the challenges of making comparisons across the nivolumab, pembrolizumab and dabrafenib+trametinib submissions, given the distinct economic modelling approaches adopted. However, in a comparative assessment of the outcomes across the models, the PBAC considered that the pembrolizumab model appeared to have resulted in an overestimate of the incremental benefits.
- 7.12 Overall, the PBAC considered that the ICER presented of \$15,000/QALY - \$45,000/QALY remained highly uncertain, variable and was most likely underestimated.
- 7.13 The PBAC considered if nivolumab was listed on the PBS for the adjuvant treatment of melanoma, it would be appropriate for pembrolizumab to be cost minimised to nivolumab. The PBAC considered if dabrafenib+trametinib was listed on the PBS for the adjuvant treatment of BRAF mutant melanoma, it would be appropriate for pembrolizumab to be cost minimised to dabrafenib+trametinib for the proportion of the population that is BRAF mutant positive.
- 7.14 The PBAC noted that the estimated financial implications of listing pembrolizumab on the PBS for use in adjuvant melanoma had been updated to exclude cost offsets compared to the November 2018 submission. The PBAC considered that the financial impact remained very high (approximately more than \$100 million per year for approximately [REDACTED] patients). The average number of administrations per patient ([REDACTED] per year) and the uptake rate (85%) remained the same as in November 2018. The PBAC noted that it had previously considered these values to be overestimations.
- 7.15 The PBAC noted that the resubmission proposed a Risk-Sharing Arrangement (RSA). The PBAC considered that, in the context of the uncertain use across the adjuvant and unresectable or metastatic settings, any proposed RSA should encompass adjuvant and unresectable use of all PD-1 inhibitors. The PBAC considered that an appropriate RSA would consist of subsidisation caps across both the adjuvant and unresectable or metastatic settings, beyond which 100% rebates would apply.
- 7.16 The PBAC considered that the subsidisation caps in the unresectable or metastatic settings should include a reduction in utilisation to account for patients receiving

adjuvant treatment that results in a cure. The PBAC noted that such a reduction in use in the unresectable setting was unlikely to be observed in the first year of the adjuvant listing; however, from the second year onwards, a reduction in use in the unresectable or metastatic setting should be accounted for.

- 7.17 The PBAC advised that any future submission should be a major submission and should provide more mature follow-up data from the KN054 trial, if available, and address the issues noted by the ESC and PBAC from this consideration and from November 2018 regarding the economic model, update the financial impact estimations and outline a proposed RSA.
- 7.18 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

MSD is disappointed with this outcome and will continue to work with the PBAC towards a PBS listing for eligible patients. More than 60% of patients are BRAF wildtype and currently do not have any treatment options recommended for reimbursement in the adjuvant setting.

PBAC has accepted that PEMBRO and NIVO are non-inferior. MSD has published an independent ITC in the Journal of Drug Assessment, (Lorenzi et al 2019) which outlines commentary on the transitivity between trials. MSD would like to note that there are molecular differences between the regimens and they cannot be considered biosimilar. Across indications, PEMBRO has higher binding affinity and produces lower anti-drug antibodies compared with NIVO.