7.05 PEMBROLIZUMAB, Solution concentrate for I.V. infusion 100 mg in 4 mL, Keytruda®, Merck Sharpe & Dohme (Australia) Pty Ltd.

1 Purpose of resubmission

1.1 The resubmission requested a Section 100 (Efficient Funding of Chemotherapy), Authority Required listing for pembrolizumab for the treatment of relapsed or refractory primary mediastinal B-Cell lymphoma (R/R PMBCL). The requested listing was unchanged from the previous submission.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care (SOC). This was the same as the previous submission.

Table 1: Key components of the clinical issue addressed by the resubmission (as stated in the resubmission)

Component	Description
Population	Relapsed or refractory primary mediastinal large B-cell lymphoma (R/R PMBCL)
Intervention	Pembrolizumab 200 mg Q3W for up to 35 cycles
Comparator	Chemotherapy regimens such as ICE, GDP or DHAP with or without rituximab.
Outcomes	PFS, OS, ORR
Clinical claim	Pembrolizumab is superior to chemotherapy regimens in improving survival and has lower toxicity. Patients who achieve a complete response, and maintain it, can be considered cured, and therefore pembrolizumab offers an improved chance of curing this disease. Pembrolizumab also provides patients with a potential bridge to allogeneic stem cell transplant.

Source: Table 1.1-1, p 14 of the resubmission.
Underlined: New addition compared to the previous submission.
DHAP = dexamethasone, high-dose cytarabine, cisplatin; GDP = gemcitabine, dexamethasone, cisplatin; ICE= ifosfamide, carboplatin, etoposide; ORR= objective response rate; OS= overall survival; PFS = progression free survival; Q3W = every three weeks.

2 Background

Registration status

2.1 Pembrolizumab was TGA registered in October 2018 for the treatment of adult and paediatric patients with refractory primary mediastinal B-cell lymphoma, or who have relapsed after two or more prior lines of therapy.

2.2 The PBAC noted that the FDA approved pembrolizumab for use in R/R PMBCL based on the Keynote 170 trial (January 2018 data cut-off). The FDA approved pembrolizumab for R/R PMBCL under accelerated approval based on tumour response rate and durability of response.[1]

[1] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-treatment-relapsed-or-refractory-pmbcl

Previous PBAC consideration

2.3 This is the second PBAC consideration of pembrolizumab for R/R PMBCL. The first submission was considered by the PBAC in November 2018. The key matters of concern are summarised below.

Table 2: Summary of key matters of concern

Component	Matter of concern (Pembrolizumab PMBCL PSD, Nov 2018 PBAC meeting)	How the resubmission addresses it
Maturity of pembrolizumab data	The PBAC considered that the data from the pembrolizumab studies were immature, with the Phase 2 KN170 study having a median duration of follow-up of 9.7 months (January 2018 data cut-off) and a large degree of censoring (para 6.25) The PBAC advised that more mature trial data would help inform a resubmission (para 7.1).	Updated OS data from KN170: New data cut-off May 2019 (median duration of follow-up 22.3 months). The pembrolizumab arm of the model was based on this additional 13 months of data from KN170.
Data for the SOC arm	The OS data for SOC were sourced from a retrospective cohort study (Kuruvilla 2008). The ESC and the PBAC considered that Kuruvilla 2008 was not representative of current clinical practice as the salvage regimens did not contain rituximab (para 6.10). The economic evaluation used a subgroup of the Kuruvilla 2008 population to estimate OS for the SOC arm (the subgroup comprised 24 of the 37 patients included in Kuruvilla 2008). The ESC and PBAC considered that it was not reasonable to select a subgroup. The ESC considered that it would have been more reasonable to use the full population of Kuruvilla 2008 (rather than a subgroup) (para 6.32). The PBAC considered that Vardhana 2018 was also a relevant source for estimating SOC chemotherapy outcomes in current practice (para 7.6)	Another retrospective cohort study (Vardhana 2018) was included in the resubmission to provide outcome estimates for SOC. In Vardhana 2018, 40% and 48% of patients received rituximab as a component of primary and second line chemotherapy, respectively. Several cohorts were identified in the Vardhana 2018 study, which the resubmission claimed better matched the target population (compared with the full study population), and used as a proxy to inform survival in the SOC arm in the model. The following combined cohorts were used in the base case economic analysis: • Patients who were refractory to second line chemotherapy but underwent ASCT (n=13); • Patients who did not undergo ASCT (n=9)
Utility values	The utility data that informed the utility values was not provided in the submission; therefore, the validity of using these data to inform the model could not be evaluated. The ESC and PBAC considered that, in the absence of data to evaluate these utilities, more conservative utility values should have been applied (para 6.38).	The resubmission stated that the utilities derived from EQ-5D scores from KN170 continued to be used in the base case, as they were trial based and therefore of most relevance to a PMBCL cohort. As in the original submission, the resubmission did not provide the quality-of-life outcomes for the EQ-5D questionnaire observed in KN170. The impact of a range of utility estimates from the published literature were tested in sensitivity analyses.

Component	Matter of concern (Pembrolizumab PMBCL PSD, Nov 2018 PBAC meeting)	How the resubmission addresses it
Prevalent population	The submission included grandfathered patients as well as a prevalent pool of patients (the relapsed 5-year prevalent population). Including prevalent patients as well as grandfathered patients (who would presumably have been drawn from the prevalent pool), and assuming that prevalent patients would "drip feed" into the treated patient group over the full six years of the analysis, was likely to have overestimated the number of eligible patients as most of these patients are likely to be treated in the first year of listing (para 6.47)	The prevalent PMBCL population was derived and calculated from the latest non-Hodgkin's Lymphoma epidemiological data (AIHW). The prevalent population are only included in the first year of listing.

Source: Pembrolizumab PMBCL PSD, Nov 2018 PBAC meeting, Section 2.5 and pp90-93 of the resubmission.
AIHW = Australian Institute of Health and Welfare; ASCT = autologous stem cell transplant; EQ-5D = EuroQol 5 dimensions; OS = overall survival; PFS = progression free survival; PMBCL = primary mediastinal B-cell lymphoma; SOC = standard of care; PSD = Public Summary Document.

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

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Dispensed Price Max Amt	Manufacturer
PEMBROLIZUMAB Injection	200 mg	~~5~~ *6*	Published[a] $8,717.46 (private); $8,559.06 (public) Effective[b] $[redacted] (private); $[redacted] (public)	Merck Sharp and Dohme Pty Ltd
Available brands				
Keytruda (pembrolizumab 100 mg/4 mL injection, 4 mL vial)				
Keytruda *(pembrolizumab 50 mg powder for injection, 1 vial)*				

Category / Program: Section 100 – Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☐Unrestricted benefit ☐Restricted benefit ☒Authority Required – In Writing Only ☐Authority Required – Telephone/Electronic/Emergency ☐Authority Required – Streamlined
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: *Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.*
Episodicity: Relapsed or refractory
Severity: [nil]

Condition: primary mediastinal B-Cell lymphoma
Indication: Relapsed or refractory primary mediastinal B-Cell lymphoma
Treatment Phase: Initial treatment
Clinical criteria
The condition must be confirmed as primary mediastinal B-Cell lymphoma through use of computed tomography (CT) and/or positron emission tomography (PET) scan and histology examination, with the results retained in the patient's medical records
AND
Clinical criteria:
Patient must have undergone an autologous stem cell transplant (ASCT*) for this condition and have experienced relapsed or refractory disease post ASCT;* ~~or~~
OR
Clinical criteria:
Patient must not be suitable for ASCT *for this condition and have experienced relapsed or refractory disease following at least 2 prior treatments for this condition*
AND
Clinical criteria:
Patient must have *received prior treatment with* ~~refractory Primary Mediastinal B-cell Lymphoma~~ ~~following~~ rituximab-based chemotherapy for this condition
AND
Clinical criteria:
Patient must have a WHO performance status of 0 or 1
AND
Clinical criteria:
Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria:
The treatment must not exceed a total of 7 doses under this restriction
Prescribing Instructions: Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; (b) a completed primary mediastinal B-Cell lymphoma pembrolizumab PBS Authority Application*, which includes:* *(i) a declaration that PET and/or CT scans and histology results supporting a diagnosis of primary mediastinal B-Cell lymphoma have been retained on the patient's medical records;* *(ii) a declaration of whether the patient's disease is relapsed or refractory, and the date and means by which the patient's disease was assessed as being relapsed or refractory.* *(iii) dates of commencement and completion of 2 prior lines of treatment for patients not suitable for ASCT, one of which must include rituximab with chemotherapy.*
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services ~~Prior Written Approval of Complex Drugs~~ Complex Drugs Reply Paid 9826 ~~GPO Box 9826~~ HOBART TAS 7001

[a] *The published prices were taken from the 1 January 2020 PBS update for the Efficient Funding of Chemotherapy Supplement*.

[b] Prices do not include additional compound fee where compounding was undertaken at a TGA-licensed compounding site ($20).

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Dispensed Price Max Amt	Manufacturer
PEMBROLIZUMAB Injection	200 mg	6	Published[a] $8,717.46 (private); $8,559.06 (public) Effective[b] $[redacted] (private); $[redacted] (public)	Merck Sharp and Dohme Pty Ltd
Available brands				
Keytruda (pembrolizumab 100 mg/4 mL injection, 4 mL vial)				
Keytruda *(pembrolizumab 50mg powder for injection)*				

Category / Program: Section 100 – Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☐Unrestricted benefit ☐Restricted benefit ☐Authority Required – In Writing ☒Authority Required – Telephone/Electronic/Emergency ☐Authority Required – Streamlined
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: *Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.*
Episodicity: Relapsed or refractory
Severity: [nil]
Condition: primary mediastinal B-Cell lymphoma
Indication: Relapsed or refractory mediastinal B-Cell lymphoma
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition
AND
~~**Prescriber instructions:**~~ ***Clinical criteria:***
The treatment must not exceed a total of 35 cycles in a lifetime
~~**Prescriber instructions:**~~ ***Administrative Advice:*** Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

[a] The published prices were taken from the 1 January 2020 PBS update for the Efficient Funding of Chemotherapy Supplement.
[b] Prices do not include additional compound fee where compounding was undertaken at a TGA-licensed compounding site ($20).

Category / Program: Section 100 – Efficient Funding of Chemotherapy

Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☐Unrestricted benefit ☐Restricted benefit ☒Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☐Authority Required – Streamlined
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: *Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.*
Episodicity: Relapsed or refractory
Severity: [nil]
Condition: primary mediastinal B-Cell lymphoma
Indication: Relapsed or refractory primary mediastinal B-Cell lymphoma
Treatment Phase: Grandfathered ~~patients~~ *treatment (initial treatment of a patient commenced on non-PBS-subsidised treatment)*
Clinical criteria:
Patient must have received non-PBS-subsidised treatment with ~~a programmed cell death-1 (PD-1) inhibitor~~ this drug for this condition prior to [date of listing on the PBS]
~~**AND**~~
~~**Clinical criteria**~~
~~Patient must have had refractory Primary Mediastinal B-cell Lymphoma following rituximab-based chemotherapy prior to receiving treatment with a PD-1 inhibitor this drug for this condition; OR~~
~~Patient must have had relapsed Primary Mediastinal B-cell Lymphoma following at least two prior treatments prior to receiving treatment with a PD-1 inhibitor this drug for this condition~~
AND
Clinical criteria
The condition must have been confirmed as primary mediastinal B-Cell lymphoma through use of computed tomography (CT) and/or positron emission tomography (PET) scan and histology examination, with the results retained in the patient's medical records prior to initiating non-PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have undergone an autologous stem cell transplant (ASCT) *for this condition and have experienced relapsed or refractory disease post ASCT prior to initiating non-PBS-subsidised treatment with this drug for this condition;* ~~or~~
OR
Clinical criteria:
Patient must not have been suitable for ASCT *for this condition and have experienced relapsed or refractory disease following at least 2 prior treatments for this condition prior to initiating non-PBS-subsidised treatment with this drug for this condition*
AND
Clinical criteria:
Patient must have received treatment with rituximab-based chemotherapy for this condition prior to initiating non-PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have had a WHO performance status of 0 or 1 prior to initiating non-PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not have received treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition prior to initiating non-PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:

Patient must not have developed disease progression while receiving treatment with ~~a PD-1 inhibitor for this *condition*~~ *this drug for this condition*
AND
Clinical criteria:
The treatment must not exceed a total of 35 cycles in a lifetime
AND
Clinical criteria:
The treatment must not exceed a total of 7 doses of PBS-subsidised and non-PBS-subsidised supply combined under this restriction
Prescribing Instructions: Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; (b) a completed Primary Mediastinal B-Cell lymphoma pembrolizumab PBS Authority Application for Grandfathered patients, *which includes:* *(i) a declaration that PET and/or CT scans and histology results supporting a diagnosis of primary mediastinal B-Cell lymphoma have been retained on the patient's medical records;* *(ii) a declaration of whether the patient's disease had relapsed or was refractory, and the date and means by which the patient's disease was assessed as being relapsed or refractory prior to initiating non-PBS subsidised treatment.* *(iii) dates of commencement and completion of 2 prior lines of treatment for patients not suitable for ASCT, one of which must include rituximab with chemotherapy;*
~~**Prescriber Instructions:**~~ ***Administrative Advice:*** Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria
Administrative Advice: *This grandfathering restriction will cease to operate from [insert date 12 months from listing date here]*
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001

3.2 The resubmission proposed a special pricing arrangement (SPA) with an effective approved ex-manufacturer price (AEMP) of $[redacted] per 100 mg vial. This was a 13.4% reduction from the AEMP of $[redacted] proposed in the previous submission.

3.3 The ESC proposed the following clinical criteria in line with the current restriction for pembrolizumab for R/R Hodgkin lymphoma:

> Patient must have refractory Primary Mediastinal B-cell Lymphoma following rituximab-based chemotherapy for this condition; OR
>
> Patient must not be suitable for autologous stem cell transplant (ASCT) or have relapsed following prior ASCT for this condition and have relapsed or refractory disease following at least 2 prior treatments for this condition,
>
> AND
>
> Patient must not have received prior treatment with a PD-1(programmed cell death-1) or PD-L1 (programmed cell death ligand-1) inhibitor for this condition
>
> AND
>
> The treatment must be the sole PBS-subsidised therapy for this condition.

The pre-PBAC response stated that the sponsor agreed with the restriction wording proposed by the ESC. The PBAC considered that the clinical criteria for patients who had undergone an ASCT should be in line with the current restriction for pembrolizumab for R/R Hodgkin lymphoma 'Patient must have undergone an autologous stem cell transplant (ASCT) for this condition and have experienced relapsed or refractory disease post ASCT'. The PBAC noted that this would be consistent with the KN170 study patient population.

3.4 The requested listing specifies prior rituximab-based therapy for refractory disease but not for relapsed disease. All patients in KN170 had prior rituximab-based therapy. In addition, the relapsed arms in the proposed clinical management algorithm (Figure 1), flow from prior rituximab-based chemotherapy. The PBAC considered that it was appropriate for the listing to specify that prior treatment must have included rituximab-based therapy for patients who are not suitable for ASCT or who have relapsed following prior ASCT.

3.5 The pre-PBAC response stated the sponsor was not supportive of the proposed inclusion of WHO performance status as a clinical criterion, highlighting that patients have few treatment options and that this is not a requirement for R/R Hodgkin's lymphoma on which the restriction is based. The PBAC agreed with the pre-PBAC response that WHO performance status was not required in the restriction.

3.6 The resubmission proposed five repeats for the initial restriction and six repeats for the continuing treatment restriction. The PBAC noted that this differs from the current listing for R/R Hodgkin lymphoma which has a maximum of six repeats in both settings. The PBAC advised that the maximum number of repeats for the initial prescription should be increased from five to six, with a maximum of six repeats for continuing therapy, so that the total corresponds to the maximum number of cycles (35) allowed overall.

3.7 The resubmission noted that no changes had been made to the initial and continuing restrictions from the previous submission. The wording of the grandfathering restriction was updated in the resubmission to allow access for patients on cost share programmes or paying privately, and patients on patient familiarisation programmes. In November 2018, the PBAC considered that the grandfather restriction should require patients to have previously received treatment with pembrolizumab, to disallow patients to switch from other non-PBS subsidised programmed cell death-(ligand) 1 (PD-(L)1) inhibitors (paragraph 2.10, pembrolizumab PMBCL Public Summary Document (PSD), November 2018 PBAC meeting). The PBAC noted that the wording of the grandfather restriction in the resubmission had not been modified accordingly and reiterated that the restriction should specify that patients must have received non-PBS-subsidised treatment with pembrolizumab.

3.8 The number of patients specified in the resubmission for grandfathering was 2 compared to 10 patients in the previous submission.

3.9 The ESC noted the TGA registered indication for pembrolizumab for R/R PMBCL included paediatric patients. The ESC considered it was appropriate for the restriction to remain agnostic on age despite the KN170 study population criteria requiring patients to be ≥ 18 years of age. The ESC advised that there was no clinical reason that R/R PMBCL patients under 18 would respond differently to pembrolizumab compared to adults.

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

4 Population and disease

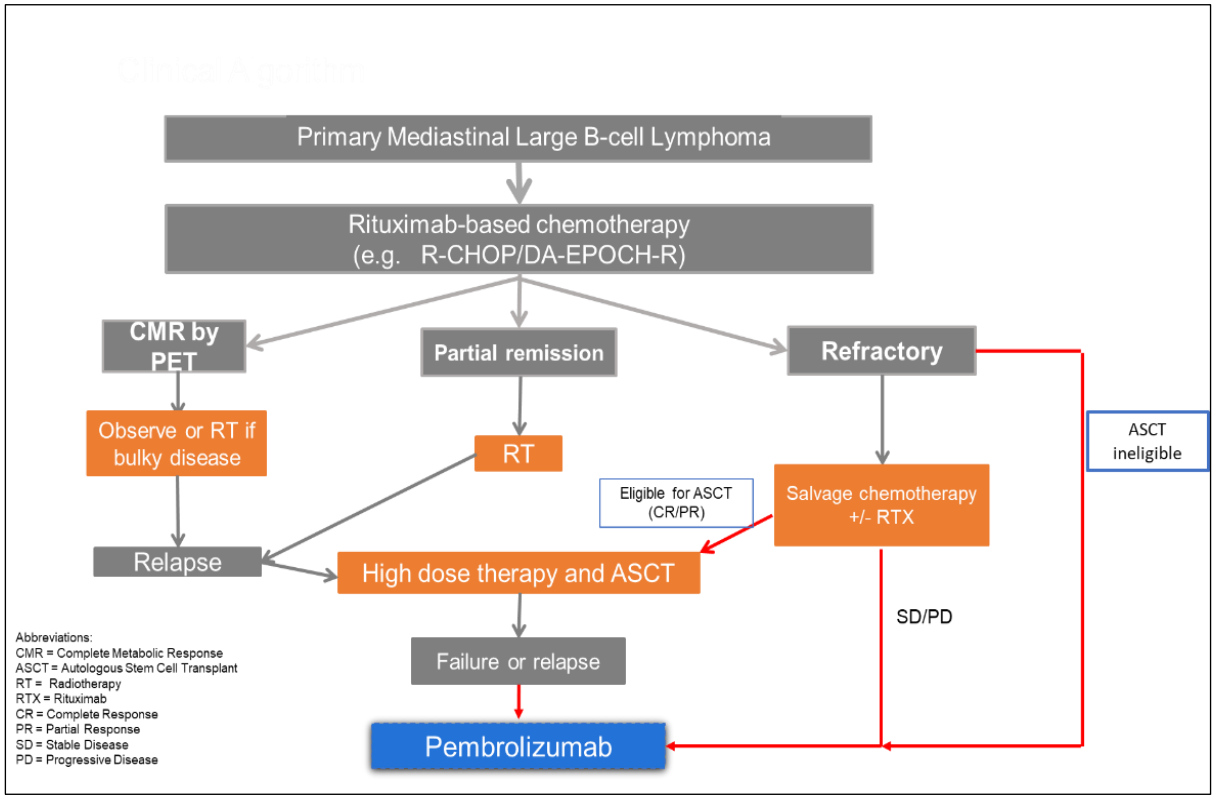
4.1 The proposed target population of R/R PMBCL was unchanged from the previous submission.

4.2 PMBCL is a rare subtype of non-Hodgkin lymphoma (nHL) and a variant of the diffuse large B-cell lymphomas (DLBCL). For patients who are refractory to initial therapy with rituximab-based chemotherapy regimens, or who have relapsed after two or more prior therapies, the prognosis is poor. The PBAC agreed with ESC that there was a high unmet clinical need for treatment options in the R/R setting for this rare condition that primarily impacts young adults.

4.3 The resubmission stated that refractory patients receiving salvage treatment with a second chemotherapy regimen were unlikely to achieve a response. For relapsed patients, a second line of chemotherapy may result in a response, which would then potentially enable them to receive HDT-ASCT. As depicted in the proposed clinical management algorithm (Figure 1), some primary refractory patients will directly be eligible for pembrolizumab (considered at the outset as "ASCT ineligible") and the remainder of the primary refractory population will be considered ineligible for ASCT (and hence eligible for pembrolizumab) only after failure to respond to salvage chemotherapy. The ESC noted that there are no guidelines for treatment of PMBCL in Australia or overseas, however the Committee considered the proposed clinical algorithm was in alignment with current clinical practice[2].

[2] Giulino-Roth, L. How I treat primary mediastinal B-cell lymphoma. Blood, 2*018 132*(8), 782-790. doi:10.1182/blood-2018-04-791566

Figure 1: Proposed clinical management algorithm with the listing of pembrolizumab for the treatment of R/R PMBCL



Source: Figure 1.2-2, p 8, of the resubmission

ASCT = autologous stem cell transplant; CMR = complete metabolic response; CR = complete response; DA-EPOCH-R = dose-adjuster etoposide, prednisolone, oncovin, cyclophosphamide, hydroxydaunorubicin and rituximab; PD = progressive disease; PET = positron emission tomography; R– CHOP = rituximab and cyclophosphamide, doxorubicin, vincristine, prednisolone; R/R PMBCL = relapsed or refractory primary mediastinal B-cell lymphoma; PR = partial response; RT = radiotherapy; RTX = rituximab; SD = stable disease.

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

5 Comparator

5.1 The resubmission nominated ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, high-dose cytarabine, cisplatin) or GDP (gemcitabine, dexamethasone, cisplatin) regimens, with or without rituximab, as the main comparator. The nominated comparator was amended in the resubmission to include rituximab-based chemotherapy, as requested by the PBAC in the previous consideration of pembrolizumab (paragraph 7.3, pembrolizumab PMBCL PSD, November 2018).

5.2 In clinical practice, heavily pre-treated R/R PMBCL patients may be unlikely to receive further salvage therapy and may either enrol in a trial or await a trial whilst receiving

definitive radiotherapy[3,4]. Best supportive care or a non-cytotoxic agent may represent a more reasonable comparator for some of these patients.

5.3 Some refractory patients would generally receive salvage treatment with a second line rituximab-containing chemotherapy regimen, while relapsed patients would generally receive second line rituximab-containing chemotherapy (high dose therapy) aiming for transplant if suitable (paragraphs 2.5 and 4.4, pembrolizumab PMBCL PSD, November 2018). Other patients who fail front line rituximab based chemotherapy may be considered unsuitable/ineligible for further chemotherapy. The proportion of these patients in clinical practice is uncertain.

5.4 The ESC advised that in clinical practice ICE, DHAP or GDP regimens would include the addition of rituximab and considered the inclusion of this agent in the resubmission appropriate for the comparator. However, the ESC also agreed with the evaluation that the appropriate comparator may vary depending on the patients PMBCL treatment history.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (8) and organisations (2) via the Consumer Comments facility on the PBS website. The comments describe a high unmet need due to the poor prognosis for patients with PMBCL who fail to achieve a complete remission or who relapse after first line chemotherapy and rituximab. The comments also highlight that this is a rare disease that has a predilection for adolescents and young adults. Comments from Lymphoma Australia and Leukaemia Foundation reiterated the need for treatment for rare aggressive diseases such as R/R PMBCL.

6.3 The PBAC noted that a letter from a group of eight haematologists estimated 15 patients per year would be eligible for treatment in Australia.

[3] Vardhana S, Hamlin PA, Yang J, Zelenetz A, Sauter CS, Matasar MJ, et al. Outcomes of relapsed and refractory primary mediastinal (thymic) large B cell lymphoma treated with second-line therapy and intent to transplant. Biology of Blood and Marrow Transplantation. 2018; 24(10):2133-8.

[4] Ng AK, Yahalom J, Goda JS, Constine LS, Pinnix CC, Kelsey CR, et al. Role of radiation therapy in patients with relapsed/refractory diffuse large B-cell lymphoma: guidelines from the International Lymphoma Radiation Oncology Group. International Journal of Radiation Oncology* Biology* Physics. 2018;100(3):652-69

Clinical studies

6.4 The resubmission was based on two single-arm studies for pembrolizumab (KN013 and updated KN170 data) and two retrospective observational single-arm studies for SOC therapies (Kuruvilla 2008 and Vardhana 2018). The inclusion of Kuruvilla 2008 in the evaluation as supporting evidence for current clinical practice was not considered to be informative as the salvage regimens did not contain rituximab. There were no new data from KN013, which had already been considered by the PBAC. Essentially, the additional evidence in the resubmission was based on a naïve indirect comparison between the following two studies:

- Pembrolizumab: Updated KN170 data (data cut-off 28 May 2019; Median duration of follow-up 22.3 months). This was a Phase II, single-arm, open label, multicentre prospective study (2014-2017) of pembrolizumab (200 mg Q3W) designed to determine the overall response rate (ORR) in heavily pre-treated patients (median prior lines of therapy = 3; range 2 – 8) with R/R PMBCL (N=53). The secondary efficacy outcomes were progression free survival (PFS), overall survival (OS), disease control rate, duration of response, safety and tolerability; and
- SOC: Vardhana 2018 (Median follow-up 4.8 years). This was a retrospective single arm study (1989 – 2014) assessing the outcomes of patients with R/R PMBCL who were administered second line chemotherapy (all patients had disease progression after front line anthracycline-based chemotherapy) with intent to consolidate with ASCT[5] (N = 60). The outcomes from subgroups of Vardhana 2018 were used as input to inform the SOC arm of the economic evaluation.

6.5 The KN013 and Kuruvilla 2008 studies included in the previous submission did not form the key evidence for the economic evaluation but were retained as part of the overall evidence in the resubmission.

6.6 Details of the studies presented in the resubmission are provided in the table below.

[5] Approximately 40% of patients in Vardhana 2018 received a rituximab-based chemotherapy regimen (R-ICE/R-CHOP, R-EPOCH) in the first-line setting, and 58% of patients were refractory to their initial therapy. Second-line chemotherapy consisted of ICE (33%) and ICE with rituximab (48%) in most cases.

Table 3: Studies and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Pembrolizumab		
Keynote-013 (KN013)	A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Patients with Hematologic Malignancies. P013V01. Zinzani, P. L., Ribrag, V., Moskowitz, C. H., Michot, J., Kuruvilla, J., Balakumaran, A., Zhang, Y., Chlosta, S., Shipp, M. A., and Armand, P. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Ribrag et al. An open-label, multicohort Phase Ib trial of pembrolizumab (MK-3475) for advanced hematologic malignancies: KEYNOTE-013.	CSR, 29 September 2017 Blood 2017; 130(3): 267-270. Journal for ImmunoTherapy of Cancer 2015; 3: (Supplement 2).
Keynote – 170 (KN170)	A Phase II Study of Pembrolizumab (MK-3475) in Patients with Relapsed or Refractory Primary Mediastinal Large B-cell Lymphoma (R/R PMBCL) or Relapsed or Refractory Richter Syndrome (rrRS). Michot et al. KEYNOTE-170: Phase II Study of Pembrolizumab in Patients with Relapsed/Refractory Primary Mediastinal Large B Cell Lymphoma (R/R PMBCL) or relapsed or refractory Richter syndrome (rrRS). Michot et al. Pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma (R/R PMBCL) or relapsed or refractory Richter syndrome (rrRS): Phase 2 KEYNOTE-170 study. Zinzani et al. Efficacy and Safety of Pembrolizumab in Relapsed/Refractory Primary Mediastinal Large B-cell Lymphoma (R/R PMBCL): Interim analysis of the KEYNOTE-170 Phase 2 Trial.	KN170 Efficacy Update Report, 19 January 2018. KN170 Safety Update Report, 19 January 2018 KN170 Efficacy Update Report, 31 July 2019 *Journal for ImmunoTherapy of Cancer* 2016; 4 (Supplement 1). *Annals of Oncology* 2016; Volume 27, Issue suppl_6, 944TiP. *Hematological Oncology* 2170; 35 (Supplement 2).
Salvage chemotherapy as standard of care (SOC)		
Kuruvilla 2008	Kuruvilla, J., Pintilie, M., Tsang, R., Nagy, T., Keating, A. and Crump, M. Salvage chemotherapy and autologous stem cell transplantation are inferior for relapsed or refractory primary mediastinal large B-cell lymphoma compared with diffuse large B-cell lymphoma.	Leukemia and Lymphoma 2008; 49(7): pp.1329-1336
Vardhana 2018	Vardhana et al. Outcomes of Relapsed and Refractory Primary Mediastinal (Thymic) Large B Cell Lymphoma Treated with Second-Line Therapy and Intent to Transplant.	*Biology of Blood and Marrow Transplantation* 2018; 24 (10), pp. 2133-2138.

Source: Modified from Tables 2.2.1 and 2.2.2, pp29-31 of the resubmission.
Underlined represents additional evidence (updated efficacy for KN170 for the May 2019 data cut-off and an additional study for SOC by Vardhana et al (2018)).

6.7 The key features of the included evidence are summarised in the table below.

Table 4: Key features of the included evidence – indirect comparison

Study	N	Design/ duration	Risk of bias[a]	Patient population	Outcomes	Use in modelled evaluation
Pembrolizumab						
KN013	21	Single-arm, OL, Phase I, MC. Median follow-up 17.1 months	High	Age 18 years and older; R/R PMBCL; ineligible for or refused ASCT (100% at baseline); prior transplant status (38.1%); prior rituximab therapy (95.2%); median number of prior therapy lines = 3 [range: 2-9].	ORR (CR, PR), DoR, PFS, OS	Not used
KN170	53	Single-arm, OL, Phase II, MC Median follow-up 22.3 mths*		Adult R/R PMBCL; ineligible for or refused ASCT (100% at baseline) prior transplant status (38.1%); prior rituximab therapy (95.2%); median number of prior therapy lines = 3 [range: 2-8].	ORR, OS, PFS	Used
SOC therapies						
Kuruvilla 2008	37	Retrospective, cohort observational, single-arm, OL Subgroup of post ASCT (n=8) Median follow-up post ASCT 1.8 years	High	Age 18 years and older; R/R PMBCL to one prior chemotherapy; referred for salvage chemotherapy and subsequent ASCT (no prior transplant); prior rituximab therapy (3%). Patients referred for salvage chemotherapy and ASCT between 1995-2004	ORR (CR, CRu, PR), OS. Subgroup of post ASCT patients: PFS and OS.	OS Used
Vardhana 2018	60	Single-arm, retrospective, Median follow-up 57.6 months (4.8 years)		R/R PMBCL who were administered second line chemotherapy, with intent to consolidate with ASCT. All patients had disease progression after front line anthracycline-based chemotherapy. Prior rituximab therapy (40%)	ORR, OS	Used**

Source: Sections 2.3-2.4 of the resubmission.

[a] Risk of bias in the context of a naïve indirect comparison between the single arm studies. MC = multi-centre; OL = open label; R/R PMBCL = relapsed or refractory primary mediastinal large B-cell lymphoma; ORR = overall response rate; ASCT = autologous stem cell transplantation; OS = overall survival; PFS = progression-free survival.

* Median follow up for the resubmission was 22.3 months for data cut-off 28 May 2019. The November 2018 submission had a median follow up of 9.7 months based on data cut-off 19 January 2018.

**The outcomes from subgroups of Vardhana 2018 were used as input to inform the SOC arm of the economic evaluation.

6.8 The basis of the clinical evidence was a naïve indirect comparison between the pembrolizumab and SOC single arm studies with no available common reference for adjustment. No formal indirect analyses were presented. In addition, there was substantial clinical heterogeneity between the studies in terms of prior lines of therapy, durations of follow-up, and disease characteristics at baseline. There were also applicability concerns regarding the studies and the target PBS population. For all intents and purposes, the risk of bias associated with the evidence used in the

resubmission to support the clinical claim was considered high. The pre-PBAC response argued that there are inherent challenges in conducting clinical trials in rare diseases, and this should be considered when evaluating pembrolizumab based on the available single arm evidence in R/R PMBCL, especially in the context of a patient population with uniformly poor outcomes.

6.9 The Pre-Sub-Committee Response (PSCR) stated that the patient populations in Vardhana 2018 and KN170 are different to the point of being mutually exclusive – with Vardhana 2018 only including patients eligible for transplant and KN170 only including patients who were not eligible for transplant. The ESC agreed with the PSCR and in addition noted the differences between Vardhana 2018 and KN170 in terms of prior lines of therapy. Vardhana 2018 excluded patients with more than 1 prior line of therapy whereas the KN170 patient population was heavily pre-treated with a median of 3 prior lines of therapy. The ESC also noted differences in the proportion of patients pre-treated with rituximab between the KN170 study (95.2% had received prior rituximab therapy) and Vardhana 2018 (40%). The ESC recalled that there is evidence that rituximab has an incremental benefit in PMBCL in the first line setting and in R/R DLBCL when used post-rituximab containing regimens (paragraph 5.3, pembrolizumab PMBCL PSD, November 2018 PBAC meeting). The ESC advised that due to the differences in the patient populations across KN170 and Vardhana 2018 the effectiveness and safety data from these studies were not directly comparable.

6.10 The ESC noted that the requested target PBS population was broader than both the KN170 and Vardhana 2018 patient populations. The ESC noted the PBS population outlined in the restriction proposed by the ESC Committee (see paragraph 3.3) would include patients with 1 prior line of therapy if primary refractory or otherwise a minimum of 2 prior lines of therapy. KN170 did not enrol patients who were refractory to one prior line of therapy (i.e. it only enrolled patients who had received at least two prior lines of therapy). This was previously considered reasonable by the PBAC given the clinical need in this population (paragraph 2.5, pembrolizumab PMBCL PSD, November 2018 PBAC meeting). In contrast, the ESC considered that Vardhana 2018 was a fair comparator for the first line salvage chemotherapy population included in the proposed PBS restriction but not for the more heavily pre-treated population encompassed by the restriction.

6.11 The evidence of effectiveness for the SOC arm of the economic evaluation was based on small subgroups (or cohorts) of patients from Vardhana 2018 who experienced uniformly poor outcomes. There was a high risk of selection bias with this approach that likely favoured pembrolizumab.

Comparative effectiveness

6.12 The resubmission noted that the key differences from the previous submission for effectiveness were:

- Updated efficacy data from KN170: New data cut-off May 2019 (median duration of follow-up 22.3 months) vs. January 2018 data cut-off in the previous submission (median duration of follow-up 9.7 months); and
- Inclusion of Vardhana 2018 as evidence of effectiveness for SOC.

6.13 ORR results from KN170 and Vardhana 2018 (whole study population) are summarised in the table below.

Table 5: Results of ORR in the KN170 and Vardhana 2018 studies

Response	Pembrolizumab KN170 N = 53 (Post ≥ 2 lines of therapy)		SOC Vardhana 2018 N = 60 (One prior line of therapy) Median follow-up: 57.6 months
	Previous PBAC consideration (November 2018) Data cut-off 19 January 2018 Median follow-up 9.7 months	Resubmission for PBAC consideration (March 2020) Data cut-off 28 May 2019 Median follow-up 22.3 months	
Complete response, n (%), [95%CI]	6 (11.3), [4.3, 23.0]	10 (18.9), [9.4, 32.0]	24 (40.0), [NR]
Partial response, n (%), [95%CI]	18 (34), [21.5, 48.3]	14 (26.4), [15.3, 40.3]	15 (25.0), [NR]
ORR (CR +PR), n (%), [95%CI]	24 (45.3), [31.6, 59.6]	24 (45.3), [31.6, 59.6]	39 (65.0), [NR]
Stable Disease, n (%), [95%CI]	5 (9.4), [3.1, 20.7]	5 (9.4), [3.1, 20.7]	7 (12.0), [NR]
Progressive disease, n (%), [95%CI]	12 (22.6), [12.3, 36.2]	12 (22.6), [12.3, 36.2]	14 (23.0), [NR]
No Assessment/Non-evaluable*, n (%), [95%CI]	12 (22.6), [12.3, 36.2]	12 (22.6), [12.3, 36.2]	0 (0), [NR]

Sources: KN170 efficacy update report (24 months); Table 5, Paragraph 6.14, Pembrolizumab PMBCL PSD, Nov 2018 PBAC meeting; Table 2.5-1, p46 of the resubmission; Table 2, p2135 of the Vardhana 2018 publication

CI = confidence interval; CR = complete response; n = number of participants with event; ORR = overall response rate; PR = partial response; NR = not reported; SOC = standard of care (ICE (ifosfamide, carboplatin, etoposide) chemotherapy was administered either with or without rituximab); Q3W = once every 3 weeks.

* Non-Evaluable includes subjects with insufficient data for assessment of response.

Results that have previously been seen by the PBAC are blue highlighted.

6.14 The ESC noted that compared to the KN170 data presented in the previous submission (January 2018 data cut-off), four patients who originally experienced a partial response (PR), were subsequently determined to have a complete response (CR) for the May 2019 data cut-off (18.9%). However, the ESC noted the overall ORR results remained the same (45.3%) with these more mature data. The PBAC agreed with the ESC that the proportion of patients with an ORR in KN170 was higher than previously reported in studies with a distinct PMBCL analysis of a heavily pre-treated population.[6]

[6] Lee C, et al. Biology and therapy of primary mediastinal B-cell lymphoma: current status and future directions Br J Haematol. 2019 Apr; 185(1): 25–41.

6.15 Noting the naïve nature of the comparison and the earlier baseline treatment setting in Vardhana 2018, compared to KN170 (second line vs. a median of 3 prior therapies (range 2-8), respectively), response rates were higher in Vardhana 2018 with 39 of 60 patients (ORR = 65%) experiencing either a PR (15%) or a CR (40%) to second line salvage therapy. The ESC reiterated that meaningful comparisons between Vardhana 2018 and KN170 were limited by the differences in the patient populations of these studies (see paragraph 6.9).

6.16 ORR results for KN013 (overall results and results for the 200 mg dose subgroup (n=11)), and Kuruvilla 2008 are summarised in the table below.

Table 6: Results of ORR across the KN013 and Kuruvilla 2008 studies

Outcome/Trial ID	Pembrolizumab KN013		SOC (Kuruvilla 2008) N = 37
	Total N = 21	200 mg Q3W N = 11	
Complete response, n (%), [95%CI]	7 (33.3) [14.6-57.0]	4 (36.4), [10.9,69.2]	1 (3), [NR]
Partial response, n (%), [95%CI]	3 (14.3) [3.0, 36.3]	1 (9.1), [0.2,41.3]	18 (34), [NR]
ORR (CR +PR), n (%), [95%CI]	10 (47.6) [25.7, 70.2]	5 (45.5), [16.7, 76.6]	9 (25), [11, 39]
Stable Disease, n (%), [95%CI]	5 (23.8) [8.2, 47.2]	1 (9.1), [0.2, 41.3]	5 (14), [NR]
Progressive disease, n (%), [95%CI]	4 (19) [5.4, 41.9]	3 (27.3), [6.0, 61.0]	22 (61), [NR]
Non-evaluable, n (%), [95%CI]	1 (4.8) [0.1, 23.8]	1 (9.1), [0.2, 41.3]	1 (3), [NR]
No Assessment, n (%), [95%CI]	1 (4.8) [0.1, 23.8]	1 (9.1), [0.2, 41.3]	NA

Source: Table 5, Paragraph 6.14, Pembrolizumab PMBCL PBAC PSD, November 2018.
Abbreviations: CI = confidence interval; CR = complete response; n = number of participants with event; N = total participants in group; NA = not applicable; NR = not reported; ORR = overall response rate; PR = partial response; SOC = standard of care
Results that have previously been seen by the PBAC are blue highlighted.

6.17 Results for PFS from the pembrolizumab studies are presented below. The median PFS in KN013 was more than twice that observed in KN170. Updated data from KN170, corresponding to a median follow-up of 22.3 months, indicated that the median PFS based on the updated data was similar to that observed with the earlier data cut (5.5 months [95% CI: 2.8; 15.1] with updated data versus 4.7 months [95% CI: 2.8, 11]). The PFS results are difficult to interpret given the small number of patients and the lack of a control arm.

Table 7: Results of PFS in the pembrolizumab studies (KN013 and KN170)

	KN013 N=21 Data cut-off April 2017 Median follow up 17.1 months	KN170 Previous PBAC consideration (November 2018) Data cut-off 19 January 2018 Median follow-up 9.7 months	KN170 Resubmission for PBAC consideration (March 2020) Data cut-off 28 May 2019 Median follow-up 22.3 months
Number (%) of PFS Events	11 (52.4)	33 (62.3)	34 (64.2)
Person-Months	209 (220)	341	623
Event Rate/100 Person-Months (%)	5.3 (5)	9.7	5.5
Median PFS (Months)[a]	10.4 (14.4)	4.7	5.5
95% CI for Median PFS [a]	(3.4, Not reached) (4.6, Not reached)	(2.8, 11.0)	(2.8, 15.1)
PFS rate at 6 Months in % [a]	64.3 (64.8)	44.8	46.7
PFS rate at 12 Months in % [a]	45.0 (51.8)	34.2	38.4
PFS rate at 24 Months in % [a]	Not reported	N/A	36.3

Source: Table 6, p14 of the KN170 efficacy update report (24 months), Table 2.5-2, p47 of the resubmission, and Section 11.1.3, Table 11.4, p14 of the KN013 CSR

CI = confidence interval; N/A = not available; PFS = progression free survival

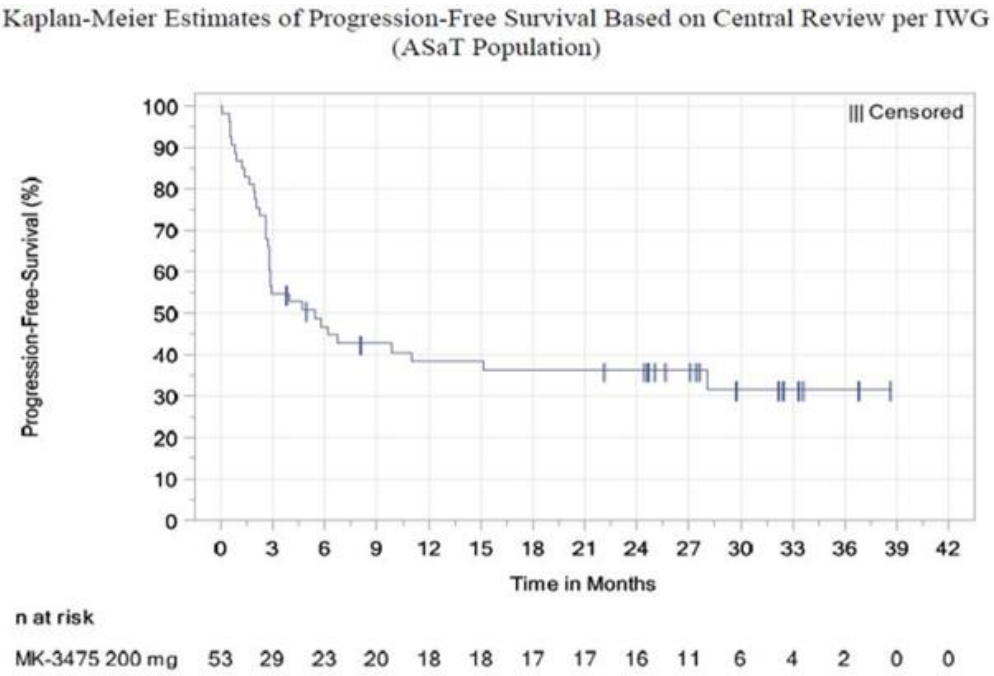
Results were inconsistent between the resubmission and the KN013 CSR (data cut-off April 2017) which was the source for the resubmission. Data from the CSR have been italicised to enable a comparison with results in the resubmission (non-italicised).

[a] From product-limit (Kaplan-Meier) method for censored data.

Results that have previously been seen by the PBAC are blue highlighted

6.18 The updated Kaplan-Meier curve of PFS from KN170 is presented below.

Figure 2: PFS Kaplan-Meier curve from KN170 (May 2019 data cut-off)



Source: Figure 2, p15 of the KN170 efficacy update report (24 months).

ASaT = All subjects as treated; IWG = International working group; PFS = progression free survival

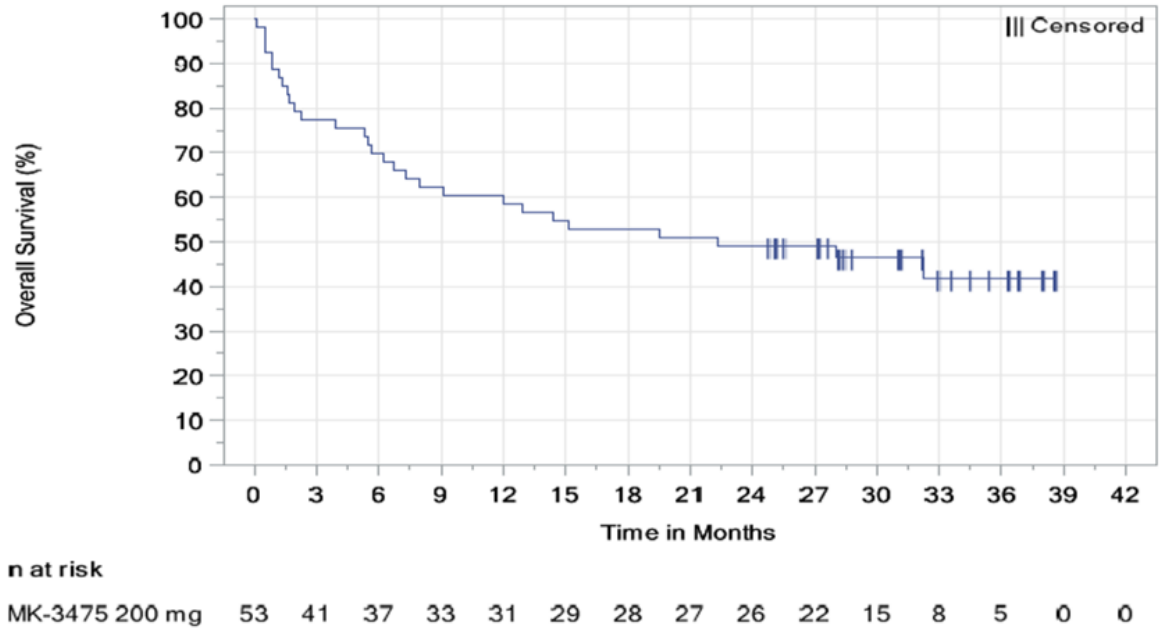
6.19 OS results from the pembrolizumab studies, including the Kaplan-Meier curve for KN170, are presented below.

Table 8: Results of OS in pembrolizumab studies (KN013 and KN170)

	KN013 Data cut-off April 2017	KN170 Previous PBAC consideration (November 2018) Data cut-off 19 January 2018 Median follow-up 9.7 months	KN170 Resubmission for PBAC consideration (March 2020) Data cut-off 28 May 2019 Median follow-up 22.3 months
Patients with event, Death n (%)	8 (38.1)	23 (43.4)	29 (54.7)
Median OS, months (95% CI) [a]	Not reached	Not reached	22.3
95% CI for Median OS [a]	(4.9, Not reached)	(7.3, Not reached)	(7.3, Not reached)
OS rate at 6 Months in % [a]	71.4%	69.8	69.8
OS rate at 12 Months in % [a]	65.9%	57.7	58.5
OS rate at 24 Months in % [a]	Not reported	N/A	49.1

Source: Table 11.5, p62 of the KN013 CSR, Table 7, p16 of the KN170 efficacy update report (24 months) accompanying the resubmission, and Table 8, Paragraph 6.19, Pembrolizumab PMBCL PSD, November 2018.
CI = confidence interval; N/A = not available; OS = overall survival.
[a] From product-limit (Kaplan-Meier) method for censored data.
Results that have previously been seen by the PBAC are blue highlighted.

Figure 3: Overall survival Kaplan-Meier curve from KN170 (May 2019 data cut-off)



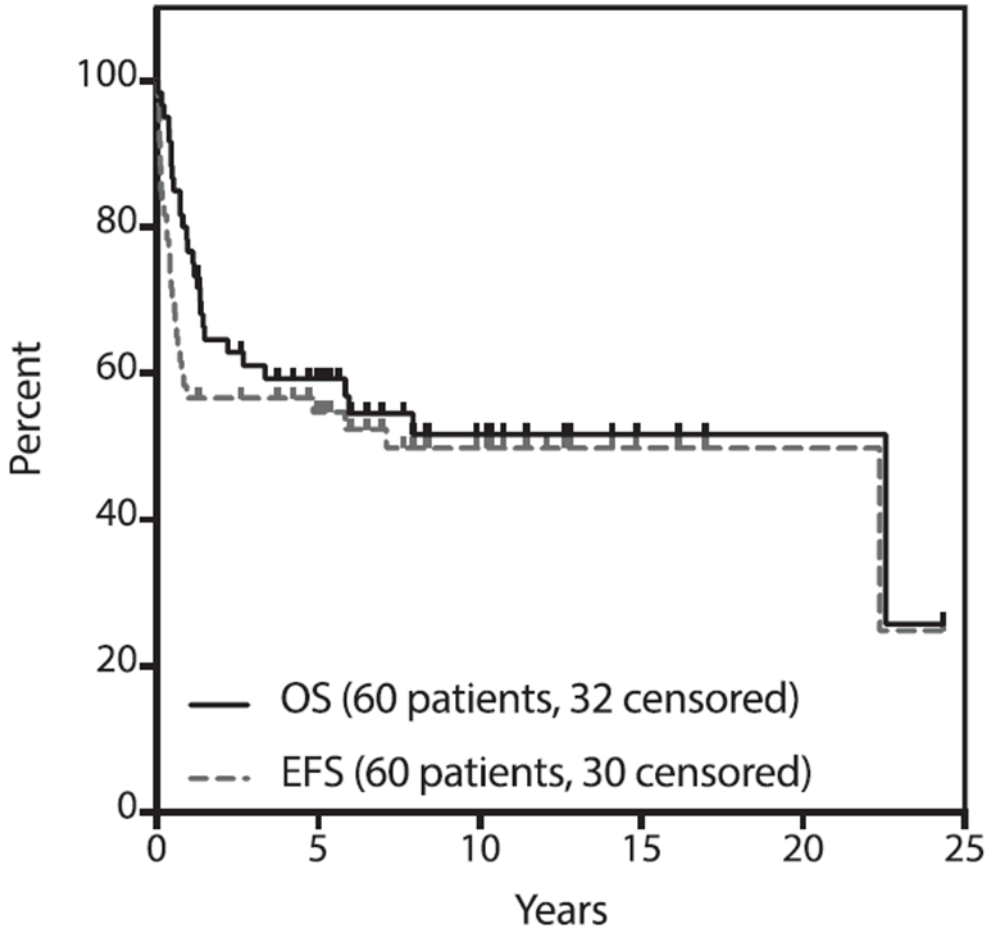
Source: Figure 3, p17 of the KN170 efficacy update report (24 months) accompanying the resubmission

6.20 The median OS was not reached for the KN170 January 2018 data cut-off. The median OS using the May 2019 data cut-off was 22.3 months (95% CI: 7.3 months, upper limit not reached). The OS rates at 6, 12 and 24 months were 70%, 60% and 49.1%,

respectively. The ESC considered that the more mature data presented in the resubmission indicated that the OS curve began to plateau at 18 months.

6.21 The median duration of follow-up for the whole Vardhana 2018 population (N = 60) was 4.8 years with an estimated 3-year OS rate of 61%. The Kaplan-Meier OS curve is presented below. For patients who proceeded to ASCT, the median follow-up from the date of SCT was 5.6 years. The estimated 3-year OS rate for these patients was 65%. Note that the survival outcome from the whole population of Vardhana 2018 was not used in the resubmission's economic model.

Figure 4: Vardhana 2018 - OS and EFS results for the whole population



Source: Figure 2.5-6, p53 of the resubmission.
OS = overall survival; EFS = event free survival.
EFS was defined from the starting second line treatment point until treatment failure, progression of disease, death from all causes, toxicity from second line therapy or HDT-ASCT requiring treatment discontinuation, or secondary malignancy, whichever came first, and patients who did not experience any of these events were censored at the date of last follow-up.

6.22 The starting time point on which the definition of OS was based differed between the KN170 and Vardhana 2018 studies. In KN170, it was the time from the first pembrolizumab dose (third or later line therapy) to death, withdrawal of consent or end of study (whichever occurred first). In Vardhana 2018, it was time from first day of second line therapy to death.

6.23 A comparison of the number of SCTs post-treatment in the KN170 and Vardhana 2018 single arm studies, are summarised in Table 9. Acknowledging the limitations of cross study comparisons, and the fact that Vardhana specifically assessed transplant-eligible patients, a total of 4 patients (7.6%) in KN170 received SCT (of whom two had an alloSCT and two had an ASCT (3.8%)) compared with 51 patients (85%) in Vardhana 2018 (of whom all received ASCT). The PSCR argued that in order to proceed to transplant, the patient must have either a complete or partial response, and the data provided supports that at least some patients would be eligible for transplant following pembrolizumab. The ESC considered that the proportion of patients reported in the KN170 study is likely to be an underestimate of the proportion going to alloSCT in the Australian population.

Table 9: Number of SCTs post-treatment in the KN170 and Vardhana 2018 single arm studies

Outcome/Trial ID	Pembrolizumab KN170 N = 53 Median follow-up 12.5 months[a]	SOC (Vardhana 2018) N = 60 Median follow-up 57.6 months (4.8 years)
Allogeneic SCT, n (%)	2 (3.8%) [a]	0 (0%)
Autologous SCT, n (%)	2 (3.8%) [a]	51 (85.0%)
Total SCT, n (%)	4 (7.6%) [a]	51 (85.0%)

Source: Table 14.1, p87 of the KN170 July 2019 CSR and Table 1, p2135 of Vardhana 2018.
n = number of participants with event; N = total participants in group; NR = not reported; SCT = stem cell therapy; SOC = standard of care.
[a] April 2018 was the most recent data cut-off for which SCT data were available from KN170 corresponding to a median follow-up of 12.5 months (0.1-25.6). It was unclear why three cases of allogeneic transplant (5.8%) were reported for the earlier January 2018 data cut-off presented in the KN170 safety update report accompanying the resubmission (Table 2.7.4-pmbcl, p45).

6.24 The resubmission argued that the study population of Vardhana 2018 was broader than the proposed PBS population, as it included a proportion of patients who underwent ASCT, and who had not relapsed by the end of follow-up. The resubmission noted that these patients would not be eligible to receive pembrolizumab under the proposed PBS restriction. To address this issue, the resubmission used OS data from subgroups of patients (or "proxies" for SOC) in Vardhana 2018 to inform the OS benefit associated with the comparator arm (see Table 12, Economic analysis).

6.25 The subgroup (Cohort C), which was used in the base case of the economic model, comprised of the following two cohorts:

- patients who were refractory to salvage therapy but underwent ASCT termed "Cohort A": n=13; OS rate at 3 years 15% (2/13) and
- patients who did not undergo ASCT termed "Cohort B": n=9; OS rate at 3 years 22% (2/9).

6.26 Thus, the base case of the economic model was informed by an OS rate at 3 years of 18% (4/22) in the SOC arm. This compares with an OS rate at 3 years of 61% in the full study population of Vardhana 2018. Pembrolizumab data were immature at 3 years, but in KN170, the OS rate at 2 years was 49%. The ESC noted the use of cohorts from Vardhana 2018 meant that survival data informing SOC was based on a very small number of patients.

6.27 Of the 9 patients in Cohort B, 8 were refractory to second line chemotherapy. These subgroups were therefore predominantly comprised of patients who were refractory to second line chemotherapy, who experienced uniformly poor outcomes in Vardhana 2018. The choice of these subgroups (or "cohorts") introduced a high risk of selection bias which most likely favoured pembrolizumab (or likely underestimated the benefit of standard practice). The PSCR argued that the differences between the populations in Vardhana 2018 and KN170 (see paragraph 6.9) meant the starting point for any comparison was highly biased against pembrolizumab. The ESC considered that the use of alternative Vardhana 2018 cohorts may have been more appropriate (see paragraphs 6.43-6.47).

6.28 The clinical data applied in the economic model is discussed in paragraphs 6.43-6.52.

Comparative harms

6.29 The resubmission noted that 1) there were no changes to the safety data from the KN170 study, and 2) there were no safety data presented in Vardhana 2018. Kuruvilla did not report safety data but the authors noted that there were no treatment-related deaths and that there were cases of febrile neutropenia (without reporting the number of cases; p1330, Kuruvilla 2008).

6.30 Similar to the November 2018 submission, the lack of safety data for SOC remained an issue in the resubmission. The PBAC previously noted that an assessment of comparative harms would have been informative and considered that it may be reasonable to base the safety of currently used SOC chemotherapies on trials in other aggressive lymphomas given the small number of patients with R/R PMBCL (Paragraph 7.7, pembrolizumab PMBCL PSD, November 2018 PBAC meeting).

6.31 The PSCR argued that the sponsor had taken a pragmatic approach to providing safety data for SOC and reviewed the PSDs for previous PBAC considerations and provided a summary of the adverse events reported (including a table adapted from the brentuximab vedotin PSD, March 2014 PBAC meeting).

6.32 The key adverse events (AEs) for the January 2018 data cut-off, which have previously been seen by the PBAC, are summarised below. More than half of patients in KN170 experienced drug-related AEs (56.6%), with a similar proportion experiencing Grade 3-5 AEs (approximately 60%). This is expected given the relapsed and refractory nature of heavily pre-treated PMBCL in the KN170 study. There were four Grade 3-5 AEs that resulted in treatment discontinuation (one event each for cardiac tamponade,

myocardial infarction, aspergillus infection and an increased aspartate aminotransferase). The most common Grade 3-5 AE was neutropenia (n = 7 (13.2%)). There were no observed deaths related to AEs.

Table 10: Summary of key adverse events in the pembrolizumab studies (KN013 and KN170)

Trial ID	KN013 N = 21	KN170 N = 53
Any AE, n (%)	20 (95.2)	49 (92.5)
Drug related AEs, n (%)	14 (66.7)	30 (56.6)
Any SAE (Grade 3 -5), n (%)	8 (38.1)	31 (58.5)
Any SAE (Grade 3-5) drug related, n (%)	5 (23.8)	13 (24.5)
AE leading to discontinuation of treatment (any grade), n (%)	1 (4.8)	4 (7.5)
AE resulting in death, n (%)	0	0

Source: Table 9, Paragraph 6.23, 6.07 pembrolizumab PMBCL PBAC PSD, November 2018 Meeting.
AE = adverse events; n = number of participants reporting data; NR = not reported; SAE = serious adverse events; SOC = standard of care.
[a] Indicated as Grade 3-5 AEs from Tables 2.5-10 and 2.5-12, pp60 and 63 of the resubmission.
[b] Treatment discontinuation: cardiac tamponade, myocardial infarction, aspergillus infection and an increased aspartate aminotransferase

Benefits/harms

6.33 The naïve indirect comparison presented in the resubmission did not allow for a quantitative comparison of the benefits and harms of pembrolizumab with SOC. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.34 The resubmission described pembrolizumab as superior in terms of effectiveness and superior in terms of safety, compared with SOC, in patients with R/R PMBCL who are ineligible to receive or have failed ASCT. It was unclear whether this claim was based on outcomes from the whole Vardhana 2018 population or the selected subgroups used in the economic analysis.

6.35 The incremental effectiveness and safety associated with pembrolizumab over SOC, could not be quantified, or assessed descriptively in a confident manner from the evidence available in the resubmission. The evidence was based on a naïve indirect comparison between pembrolizumab and SOC using two single arm studies, with no formal statistical analysis conducted, and with important clinical heterogeneity between the studies and the proposed Australian setting.

6.36 Acknowledging the limitations of the KN170 data the ESC advised that pembrolizumab appears to show effectiveness in the R/R PMBCL third line treatment setting where patients may have no other potentially curable options available. Given that PMBCL is a relatively rare condition the ESC considered that more robust pembrolizumab clinical trial data is unlikely to be forthcoming.

6.37 The superior comparative effectiveness claim was however considered by ESC to be highly uncertain based on the evidence provided as the KN170 and Vardhana 2018 studies were conducted in different R/R PMBCL populations. In addition to not reflecting the KN170 population, the ESC suggested the Vardhana 2018 study population did not reflect that of the broader proposed Australian setting. The ESC

advised that more robust comparative data was not currently available and was unlikely to become available due to the small number of patients with R/R PMBCL.

6.38 The resubmission used outcome data from subgroups in Vardhana 2018, which was comprised almost entirely of patients who were refractory to second line therapy, to represent the effectiveness of SOC. These patients experienced poorer outcomes compared to the whole study cohort as response to second line therapy was the single greatest predictor of OS in Vardhana 2018. The ESC agreed with the evaluation that this approach was likely to have underestimated the effectiveness of standard practice.

6.39 The ESC considered that AE data from the KN013 and KN170 studies add to the body of evidence regarding the toxicity profile of pembrolizumab. However, the ESC agreed with the evaluation that the comparative safety claim was unable to be quantified from the evidence presented in the resubmission.

6.40 The PBAC considered that the claim of superior comparative effectiveness was uncertain but likely reasonable in the context of this being a rare sub-type of nHL with a low incidence.

6.41 The PBAC considered although the claim of superior comparative safety may be reasonable the magnitude of any benefit could not be quantified as there was no safety data presented in Vardhana 2018.

Economic analysis

6.42 The resubmission presented a modelled economic evaluation based on a naive indirect comparison of a single arm study (KN170) and a retrospective cohort study (Vardhana 2018). The type of economic evaluation presented was a cost-utility analysis. The key components of the economic evaluation, as summarised below, were unchanged from those in the November 2018 submission.

Table 11: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Pembrolizumab versus SOC
Time horizon	10 years in the model base case versus median follow-up of 22.3 months in KN170
Outcomes	LYG and QALYs
Methods used to generate results	Partitioned survival model (i.e. area under the curve)
Health states	Progression free survival (PFS) Progressive disease (PD) Death
Cycle length	Three weeks (in line with the duration of the pembrolizumab treatment cycle).
Allocation to health states	Health state allocation over time was determined from progression free and overall survival curves. Pembrolizumab: Updated KM data (May 2019 data cut-off) were used to 30 months (median follow-up 22.3 months, range 0.1-39.1 months). This was updated from the previous submission. Previous submission extrapolated survival outcome from the last observation of January 2018 KN170 data (median follow-up 9.7 months). SOC: OS data were obtained from digitised OS curves. PFS data were generated assuming the same ratio of OS:PFS as that observed for pembrolizumab. The approach was unchanged from the previous submission, although the data source was changed.
Extrapolation method	Log-logistic parametric model fitted to both treatment arms in the base case for both OS and PFS, based on visual inspection and R-squared test statistic. An ongoing treatment effect was assumed and there was no convergence of the survival curves within the modelled time horizon. This was unchanged from the previous submission. In the pembrolizumab arm, approximately 58% of QALYs and 1% of costs occurred in the extrapolated period (from 30 months). In the SOC arm, approximately 32% of QALYs and 1% of costs occurred in the extrapolated period (from 36 months for Cohort C).
Health related quality of life	Utility values for progression-free and progressed disease states were sourced from KN170. This was unchanged from the previous submission.
Selection of cohorts in Vardhana 2018 as the proxy for the OS outcome of SOC	Cohort C from Vardhana 2018 was used in the base case of economic evaluation. Cohort C consisted almost entirely of patients who were refractory to second line therapy, and represented a subgroup of the proposed PBS population with a relatively poor prognosis.

Source: Table 3.1-1 p93, Section 3.3.2.2. p119, Section 3.4.2 p123, and Section 3.4.2.1 p123-4 of the resubmission.
KM = Kaplan-Meier; LYG = life years gained; OS = overall survival; PD = progressive disease; PFS = progression free survival; QALY = quality-adjusted life-years; SOC = standard of care.

Clinical data applied in the economic model

6.43 As discussed above, the resubmission identified a number of patient cohorts in Vardhana 2018 in an attempt to determine the most appropriate outcome data to be applied in the SOC arm of the economic model (Table 12).

Table 12: Patient cohorts in Vardhana 2018 considered by the resubmission as potential proxies for the SOC arm

Cohort	Definition/ OS at 3 years	Comment in resubmission/ Applicability[a]	Use in the model
C n=22	Combination of: patients who were refractory to salvage therapy but underwent ASCT (Cohort A), and patients who did not undergo ASCT (Cohort B) OS at 3 years: 4/22 (18%)	Patients in Cohort A are unlikely to have been considered for ASCT in the Australian setting. 7 of the 9 patients in Cohort B were refractory to first line chemotherapy and 8 of the 9 patients were refractory to second line chemotherapy (1 patient was eligible for, but refused, ASCT)[b]. Both Cohort A and B represented subgroups of the proposed PBS population with a relatively poor prognosis. The combined cohort was not representative of the entire proposed PBS population, and its use is likely to have underestimated the outcomes associated with standard practice.	This cohort was used to inform the SOC arm in the base case of the model. The OS curve for Cohort C was constructed by assuming the same shape as that for Cohort E, adjusting for the 3-year survival rate.
D n=31	Patients who were refractory to first line chemotherapy OR had advanced Ann Arbor stage disease (stage III-IV) at first relapse[c] OS at 3 years: 63%[d]	Included a proportion of patients who were primary relapsed rather than primary refractory and not necessarily chemo-insensitive to second line therapy. The resubmission stated that the use of this cohort was likely to highly overestimate OS because many patients in this group received ASCT.	Not used in the economic model. No sensitivity analysis provided for this cohort.
E n=14	Patients who were refractory to first line chemotherapy AND had advanced Ann Arbor stage disease at first relapse[c] OS at 3 years: 21%[d]	Poor prognosis factors for response to salvage and OS. As acknowledged by the resubmission, these patients were those who responded poorly to second line chemotherapy. The resubmission stated that the use of this cohort was likely to overestimate OS. The exclusion of all patients who responded to first line therapy but who subsequently relapsed and would potentially have been eligible for pembrolizumab is likely to have underestimated the benefits associated with standard practice.	A sensitivity analysis based on Cohort E was provided.

Source: Table 3.3-1, pp117-118 of the resubmission.
ASCT = autologous stem cell transplantation; OS = overall survival; SOC = standard of care.
[a] As stated in the resubmission
[b] In Cohort B, 2 patients were alive at last follow-up: 1 who was eligible for but refused ASCT, and 1 who was treated with an immune checkpoint inhibitor.
[c] Refractory response to first line chemotherapy and advanced Ann Arbor stage disease at first relapse were independently associated with inferior OS. Cohort D consisted of patients with one (and only one) of these two prognostic factors, while Cohort E was comprised of patients with both prognostic factors. Therefore, these cohorts were mutually exclusive.
[d] Estimated from Kaplan-Meier plot (Figure 3 of Vardhana 2018)

6.44 Survival data for Cohort C from Vardhana 2018 were used in the base case of the economic evaluation. Cohort C was comprised almost entirely of patients who were refractory to second line therapy. Thirteen patients underwent ASCT and 9 did not undergo ASCT (8 of the 9 were refractory to second line salvage therapy). The PBAC considered that patients who were refractory to second line therapy would not undergo ASCT in the Australian setting but would be eligible for pembrolizumab under the proposed restriction.

6.45 Cohort C excluded all patients who responded to second line chemotherapy and proceeded to ASCT, the stated intent of treatment in Vardhana 2018. A proportion of these patients would have relapsed subsequent to ASCT, and would have been eligible for pembrolizumab under the requested restriction. As Vardhana 2018 reported that response to second line chemotherapy was the single greatest predictor of OS, with refractory patients having uniformly poor outcomes, the use of Cohort C is likely to have underestimated the effectiveness of SOC. In addition, the ESC considered that Cohort C represented only a small proportion of the proposed PBS population.

6.46 The resubmission stated that the OS curve for Cohort D (patients who were either primary refractory OR Ann Arbor stage III-IV) was highly likely to overestimate survival outcomes for SOC in the targeted patient population. While the model allowed sensitivity analyses to be performed based on Cohorts A, B and E, survival data for Cohort D and the full study population were not provided in the model.

6.47 Refractory response to first line chemotherapy and advanced Ann Arbor stage disease at first relapse were independently associated with inferior OS in Vardhana 2018. Cohort D consisted of patients with one (and only one) of these two prognostic factors, while Cohort E comprised patients with both prognostic factors. Hence, Cohort D and Cohort E (primary refractory AND Ann Arbor stage III-IV) were mutually exclusive cohorts. The combination of these cohorts would comprise all patients who were refractory to first line chemotherapy, plus patients who relapsed following first line therapy but had advanced Ann Arbor stage disease at first relapse (n=45). While it is acknowledged that not all of these patients would have been eligible for pembrolizumab, sensitivity analyses based on Cohort D or combined Cohorts D+E would have provided more conservative estimates of the incremental effectiveness of pembrolizumab over SOC, compared with the use of Cohort C, and may have been informative. The PSCR argued that the patient population in Cohort D was vastly different to the KN170 study participants. Therefore, the Sponsor purported that using the OS data for Cohort D would result in pembrolizumab being dominated by SOC, as a result of a significant proportion going on to receive, and respond to ASCT. The ESC agreed with the evaluation that the combination of OS data from Cohort D and Cohort E may be more reflective of the KN170 population. The pre-PBAC response disagreed with the premise that Cohorts D and E may better reflect the KN170 population arguing at least 36 of the 45 patients (80%) in Cohorts D and E received an ASCT. The pre-PBAC response stated that to compare Cohorts D and E with the KN170 population unfairly biases against pembrolizumab.

6.48 The PBAC considered that the use of the different cohorts from Vardhana 2018 did not address the fact that the study population in KN170 represented a more treatment experienced population than that in Vardhana 2018, or that the survival outcomes in the two studies were determined from different time-points.

6.49 Updated PFS and OS data from KN170 were used in the pembrolizumab arm. As PFS data were not reported in Vardhana 2018, the PFS curve for the SOC arm was

constructed by assuming that the ratio of OS to PFS observed for pembrolizumab in KN170 also applied to SOC. This approach was also used in the original submission. The resubmission did not provide any evidence to justify this approach. Not only does this implicitly assume that PFS is a valid surrogate for OS for patients with R/R PMBCL receiving immunotherapy, but it also assumes that the same relationship between PFS and OS holds for both immunotherapy and chemotherapy. There is increasing evidence to suggest that PFS is not a reliable surrogate for OS in many oncology settings, especially for immunotherapies[7,8,9]. Therefore, the validity of the PFS data generated using this approach was highly uncertain.

6.50 Vardhana 2018 only presented Kaplan-Meier curves for OS for Cohorts D and E. The survival data for Cohort E was obtained by digitising the Kaplan-Meier curve presented in Vardhana 2018. OS curves for Cohorts A, B and C were constructed based on 3-year survival rates of 15.4%, 22.2% and 18.2%, respectively, and by assuming the same shape of curve as that for Cohort E. The ESC agreed with the evaluation that while there were uncertainties inherent in this approach, a much larger concern was the appropriateness of using these patient cohorts as proxies in the SOC arm.

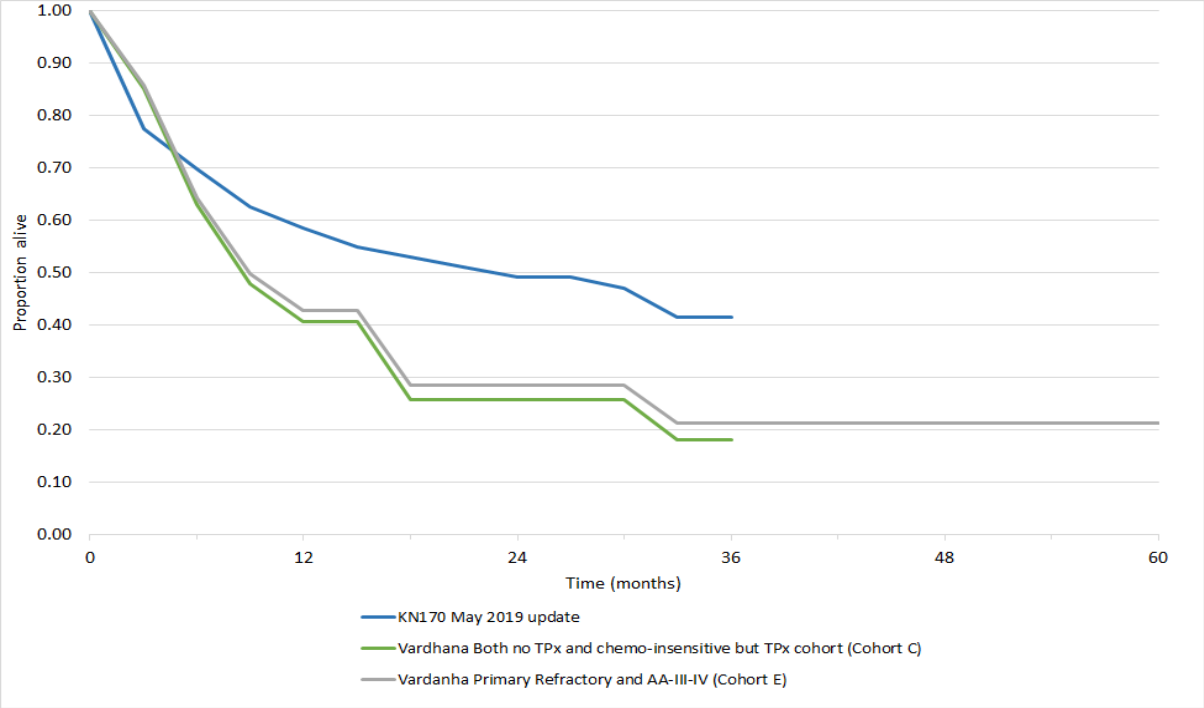
6.51 The observed OS curves for the full study population in KN170 and for Cohort E from Vardhana 2018, as well as the constructed OS curve for Cohort C from Vardhana 2018, are presented below.

[7] Buyse M, Burzykowski T, Saad ED. The search for surrogate endpoints for immunotherapy trials. Annals of translational medicine. 2018; 6(11):231.

[8] Haslam A, Hey SP, Gill J, Prasad V. A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology. Eur J Cancer. 2019 Jan; 106:196-211.

[9] Kumar S, Rajkumar SV. Surrogate endpoints in randomised controlled trials: a reality check. Lancet. 2019 Jul 27; 394(10195):281-3.

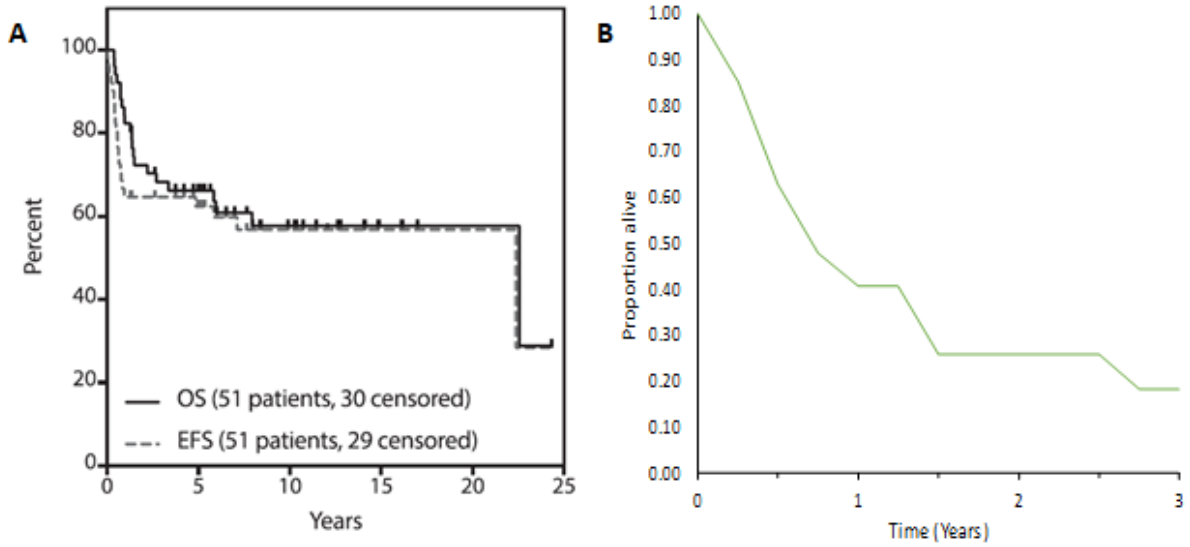
Figure 5: Observed and constructed OS outcomes from KN170 and Vardhana 2018



Source: Figure 3.3-5, p120 of the resubmission; Excel workbook 'Pembrolizumab Section 3 model November 2019.
AA = Ann Arbor stage; OS = overall survival; TPx = stem cell transplant
Data for Cohort E from Vardhana 2018 have been truncated at 60 months.

6.52 Figure 6 presents a comparison of the observed OS data for the full study population in Vardhana 2018 and the constructed OS data for Cohort C.

Figure 6: Comparison of the observed OS data for the full study population (A) and the constructed OS data for Cohort C (B) in Vardhana 2018.



Source: Figure 1, p2136 Vardhana 2018; Figure 3.3-5, p120 of the resubmission; Excel workbook 'Pembrolizumab Section 3 model November 2019.
OS = overall survival; EFS = event free survival

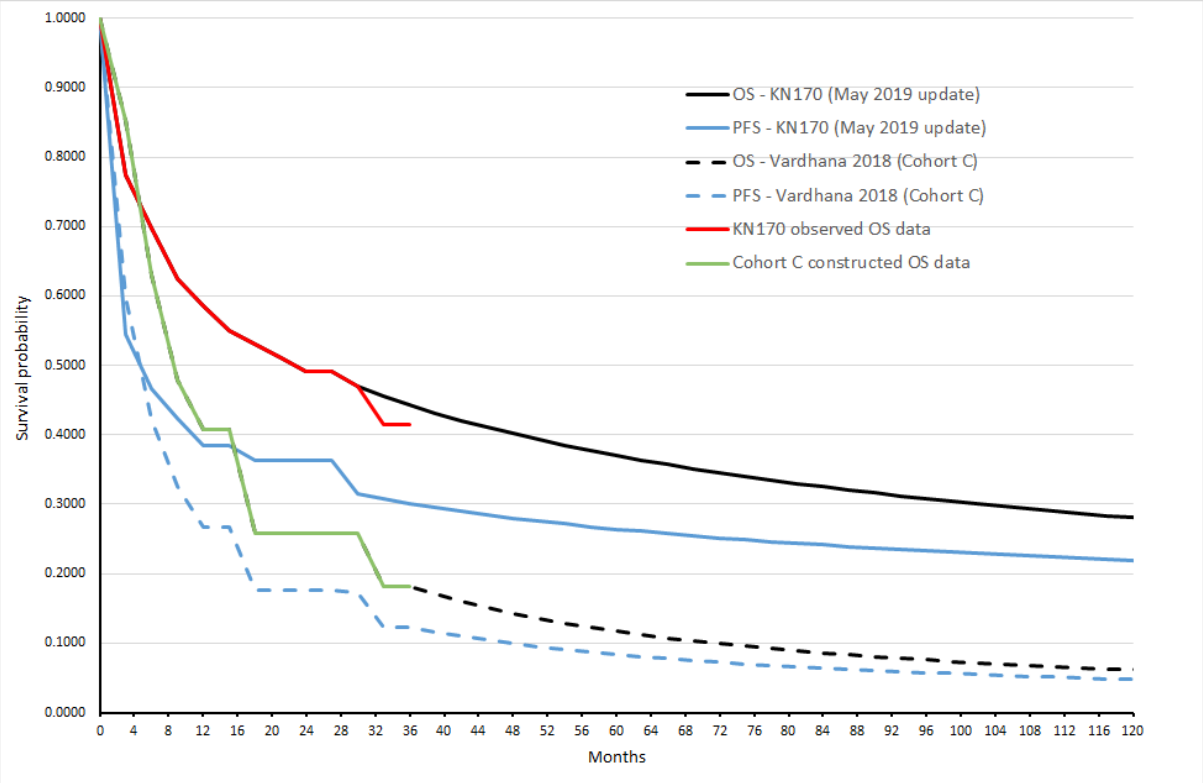
Extrapolation

6.53 Health state membership for the pembrolizumab arm was based on the observed PFS and OS Kaplan-Meier data from KN170 up until 30 months. Beyond 30 months, the PFS and OS curves were extrapolated using parametric survival distributions. The resubmission stated that the survival curves were extrapolated from a time point at which the number of patients at risk of an event became unreliably low, rather than the last observation point as in the previous submission. The resubmission did not provide any further justification for the choice of this point of extrapolation. However, the choice of time point for extrapolation had minimal impact on the incremental cost-effectiveness ratio (ICER).

6.54 Given the limited applicability of the cohorts from Vardhana 2018 used in the resubmission, the small sample size on which these extrapolations were based (Cohort E, n=14), and the subsequent 'generation' of OS data for Cohort C, the validity of the extrapolated OS data for SOC was highly uncertain. For the modelled PFS curve for SOC, this uncertainty was amplified by concerns regarding the method used to generate PFS data from the OS data, as described above.

6.55 As in the original submission, in the base case, the survival outcomes did not converge within the 10 year time horizon of the model, although convergence of the curves was applied in a sensitivity analysis. At 10 years follow-up, the absolute OS in the pembrolizumab arm was 28.1%, compared with 6.1% in the SOC arm, an absolute difference of 21.9%.

Figure 7: Extrapolation of the OS (black lines) and PFS (blue lines) curves in the base case economic model



Source: Figure 3.4-8, p129 of the resubmission; Excel spreadsheet 'Chart_Survival Curves', Excel workbook 'Pembrolizumab Section 3 model November 2019'.
OS = overall survival; PFS progression free survival

6.56 The ESC and the PBAC previously considered that the estimated ongoing treatment effect was highly uncertain as it was based on immature data that were subject to a high degree of censoring (paragraph 6.36, pembrolizumab PMBCL PSD, November 2018 PBAC meeting). While the resubmission provided updated PFS and OS data from KN170 (median follow-up 22.3 months vs 9.7 months in the previous submission), there were limited data to support the estimated ongoing treatment effect for pembrolizumab beyond 24 months, the maximum duration of treatment with pembrolizumab, with extensive censoring beyond this point. Therefore, the magnitude of any continued treatment effect beyond this time-point was still subject to uncertainty. The PSCR argued that the more mature data from KN170 that was presented in the resubmission model provided further support and greater certainty in modelling an ongoing treatment effect for pembrolizumab over the 10-year time horizon. The ESC considered that a 7.5 year time horizon was more appropriate given the limited data.

6.57 Another factor contributing to the failure of the survival curves to converge was the likely overestimation of the rate of progression and death in the SOC arm resulting from the use of a subgroup of the proposed PBS population with a relatively poor prognosis (Cohort C). Given the substantial limitations in the clinical evidence, and the inability to accurately determine which patients in Vardhana 2018 would have been

eligible for treatment with pembrolizumab, it may have been more appropriate to use a more conservative patient cohort, or the entire study population, of Vardhana 2018 in the base case of the model.

6.58 The key drivers of the model are summarised below.

Table 13: Key drivers of the model

Description	Method/Value	Impact
OS estimate for the SOC arm	OS data for Cohort C from Vardhana 2018 were used in the base case.	High, favours pembrolizumab
Extrapolation	Assumption of continued treatment effect	High, favours pembrolizumab

Source: Section 3.9 of the resubmission
OS = overall survival; SOC = standard of care.

6.59 The results of the economic evaluation are summarised below.

Table 14: Results of the economic evaluation

Component	Pembrolizumab	SOC	Increment
Current resubmission			
Costs	$	$	$
Life years	3.4780	1.7198	1.7582
Incremental cost per LY gained			$
QALYs	2.6048	1.2863	1.3184
Incremental cost per QALY gained			**$**
Previous submission			
Costs	$	$	$
Life years	3.5179	0.8013	2.7166
Incremental cost per LY gained			$
QALYs	2.7186	0.6854	2.0332
Incremental cost per QALY gained			**$**

Source: Table 3.8-1, p147 of the resubmission; Table 13, paragraph 6.40, pembrolizumab rrPMBCL, PBAC PSD, November 2018 PBAC meeting; Table 3.8.1, 6.07 Pembrolizumab (rrPMBCL) COM November 2018 PBAC meeting.
LY = life-years; QALY = quality-adjusted life-years; SOC = standard of care

The redacted table shows an ICER in the range of $45,000 to < $55,000/QALY for the current submission; and an ICER in the range of $35,000 to < $45,000/QALY for the previous PBAC consideration.

6.60 The ESC considered that the results of the model were not reliable with the key issue the uncertainty associated with the survival data for SOC due to the limited applicability of the Vardhana 2018 cohorts and the small sample sizes on which the extrapolations for OS were based.

6.61 The results of key sensitivity analyses are summarised below.

Table 15: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALYs	ICER $/QALY
Base case	$ [redacted]	**1.3184**	$ [redacted]
Univariate analyses			
Time horizon (base case 10 years)			
• 2.5 years	$ [redacted]	0.2733	$ [redacted]
• 5 years	$ [redacted]	0.6892	$ [redacted]
• 7.5 years	$ [redacted]	1.0323	$ [redacted]
Population SOC arm (base case Cohort C Vardhana 2018)[a]			
• Cohort A (refractory 2L but underwent ASCT)	$ [redacted]	1.4241	$ [redacted]
• Cohort B (no ASCT)	$ [redacted]	1.1658	$ [redacted]
• Cohort E (refractory 1L and Ann Arbor Stage III-IV)	$ [redacted]	1.0920	$ [redacted]
• Kuruvilla 2008 subgroup[b]	$ [redacted]	2.0026	$ [redacted]
• Kuruvilla 2008 whole population	$ [redacted]	1.6591	$ [redacted]
Extrapolation			
Convergence of survival curves (base case no convergence)			
• From 3 to 10 years	$ [redacted]	0.9764	$ [redacted]
• From 3 to 7.5 years	$ [redacted]	0.7473	$ [redacted]
Extrapolation PEMB (base case log-log extrapolation)			
• Weibull extrapolation	$ [redacted]	1.2240	$ [redacted]
• Lognormal	$ [redacted]	1.3185	$ [redacted]
• Gamma	$ [redacted]	1.4694	$ [redacted]
Extrapolation SOC (base case log-log extrapolation)			
• Weibull extrapolation	$ [redacted]	1.4093	$ [redacted]
• Exponential extrapolation	$ [redacted]	1.5507	$ [redacted]
• Lognormal	$ [redacted]	1.3439	$ [redacted]
• Gamma	$ [redacted]	1.2411	$ [redacted]
Extrapolation: pembrolizumab Weibull, SOC Gamma	$ [redacted]	1.1459	$ [redacted]
Utility values (base case PFS 0.797, PD 0.623, KN170 INV)			
• KN170 IRC: 0.797 and 0.654	$ [redacted]	1.3326	$ [redacted]
• Blommestein 2014: 0.88 and 0.78	$ [redacted]	1.4993	$ [redacted]
• Doordujin 2005: 0.70 and 0.45	$ [redacted]	1.1108	$ [redacted]
Assuming a proportion of patients in the SOC arm receive rituximab in combination with chemotherapy (base case 0%)[c]			
• 48% (% in Vardhana 2018 who received rituximab-based second line therapy)	$ [redacted]	1.3184	$ [redacted]
• 100%	$ [redacted]	1.3184	$ [redacted]
Multivariate analyses			
Cohort E SOC arm and Weibull extrapolation PEMB arm	$ [redacted]	0.9966	$ [redacted]
As above plus Gamma extrapolation SOC arm	$ [redacted]	0.9262	$ [redacted]

Source: Table 3.8-2 p148, and Table 3.9-1 pp150-151 of the resubmission; Excel workbook 'Pembrolizumab Section 3 model November 2019'

1L = first line; 2L = second line; ASCT = autologous stem cell transplantation; ICER = incremental cost-effectiveness ratio; INV = investigator definition; IRC = Independent Review Committee definition; PD = progressive disease; PFS = progression free survival; PEMB = pembrolizumab; QALY = quality-adjusted life-years; SOC = standard of care.

[a] Parametric extrapolation applied from 36 months for Cohorts A, B and C, and from 48 months for Cohort E.

[b] Used for base case economic evaluation in previous submission

[c] Assuming a rituximab dose of 375 mg/m^2 (675 mg assuming an average body surface area of 1.8 m^2), requiring 700 mg per dose at an AEMP of $239.87 for 100 mg, and assuming 100% dispensed in the public setting. Rituximab administered on Day 1 of each cycle, for 3 cycles of rituximab+DHAP (as recommended in the eviQ regimen), 2.5 cycles of rituximab+ICE (as for ICE in base case), and 4 cycles of rituximab+GDP (as for GDP in base case). It was assumed that the addition of rituximab to each regimen did not change the administration cost per cycle.

The redacted table shows ICERs in the range of $35,000 - < $255,000/QALY.

6.62 Sensitivity analyses indicated that the model was most sensitive to the time horizon of the model, convergence of the survival curves, and the cohort of patients from Vardhana 2018 used to determine survival in the SOC arm.

6.63 As discussed above, the sensitivity analyses provided in the resubmission did not allow assessment of the full extent of uncertainty inherent in choice of the cohort of patients from Vardhana 2018, as digitised survival data for the full study population and Cohort D were not provided. As previously stated, the PSCR argued that the patient population in Cohort D was vastly different to the KN170 study participants. The PSCR argued that as OS in Cohort D (63% at 3 years) was superior to that of pembrolizumab treated patients in KN170 (44% at 3 years) any sensitivity analysis of the economic model using these largely spurious comparative data would result in pembrolizumab being dominated by SOC.

6.64 Applying linear convergence of the OS and PFS curves for pembrolizumab with those for SOC, over the period from Year 3 to Year 10, increased the ICER to $55,000 to < $75,000 per quality-adjusted life-year (QALY) gained. When convergence was applied from Year 3 to Year 7.5, the ICER increased to $75,000 to < $95,000/QALY. It may have been conservative to extrapolate the pembrolizumab survival data using a Weibull parametric function, and that for SOC using a Gamma function; this resulted in an ICER of $55,000 to < $75,000/QALY when Cohort C from Vardhana 2018 was used in the SOC arm, and increased to $55,000 to < $75,000/QALY when Cohort E was used.

6.65 Reducing the time horizon of the model to 7.5 years increased the estimated ICER to $55,000 to < $75,000/QALY gained.

6.66 The PBAC noted that the Sponsor had not provided the quality of life outcomes for the EQ-5D questionnaire observed in KN170, although utilities derived from these scores continued to be used in the base case. The PBAC noted that the impact of a range of utility estimates from the published literature were tested in the sensitivity analysis.

Drug cost/patient/course

6.67 The mean cost/patient/course of pembrolizumab in the model was $[redacted]. This was based on a dose of 200 mg every 3 weeks, for a maximum of 35 doses (2 years), a proposed effective AEMP of $[redacted] per 100 mg vial, and assuming an average of 16.1 cycles per patient. The mean number of cycles per patient was derived from the restricted mean PFS over the first 2 years of the model, and was based on Kaplan-Meier data for PFS from KN170. This was reasonable.

6.68 The mean cost/patient/course for the SOC regimens DHAP, ICE and GDP was estimated as $2,987 in the economic model and $3,601 in the financial estimates. These costs were based on the eviQ dosing recommendations for each regimen, assuming equal proportions of treated SOC patients received each regimen, and that patients received 4 cycles of DHAP, 4 cycles of GDP, or 2.5 cycles of ICE. The

discrepancy in the cost of SOC between the model and the financial estimates is discussed below. The resubmission did not include the cost of rituximab, despite this being included as a potential component in the nominated comparator.

Table 16: Drug cost per patient for proposed and comparator drugs

	Pembrolizumab			SOC		
	Study dose and duration	**Model**	**Financial estimates**	**Study dose and duration**	**Model**	**Financial estimates**
Mean dose	200 mg/cycle	200 mg/cycle	200 mg/cycle		As per eviQ regimens	As per eviQ regimens
Mean duration	10.8 cycles (truncated mean) [a]	16.1 cycles	16.1 cycles	R-ICE ICE O-DHAP ICEMAN (doses and durations NR)	DHAP: 4 cycles ICE: 2.5 cycles GDP: 4 cycles	DHAP: 4 cycles ICE: 2.5 cycles GDP: 4 cycles
Cost/patient/cycle	$[redacted] [b]	$[redacted] [b]	$[redacted] [b]	NR	DHAP: $1,094 [e] ICE: $1,367 [e] GDP: $291 [e]	DHAP: $1,309 [e] ICE: $1,326 [e] GDP $564 [e]
Cost/patient/ /course	$[redacted] (based on truncated mean) [a]	$[redacted] [c, d]	$[redacted] [d]	NR	$2,987 [e, f]	$3,601 [e, f]

Source: Table 12-1, p47 of KN170 CSR; Tables 1 and 2, p2135 of Vardhana 2018; Table 3.6-1 p137 and Table 4.2-9 p166 of the resubmission; Excel workbook 'Pembrolizumab Section 3 model November 2019'.

DHAP = dexamethasone, high-dose cytarabine, cisplatin; GDP = gemcitabine, dexamethasone, cisplatin; ICE= ifosfamide, carboplatin, etoposide; ICEMAN = ICE + methotrexate, cytarabine; NR = not reported; O-DHAP = ofatumumab, dexamethasone, high-dose Ara-C (cytarabine), cisplatin; R-ICE = rituximab + ICE; SOC = standard of care.

[a] Truncated mean duration of treatment in KN170 (data cut-off April 2018). The cost/patient/course based on this input will be an underestimate (see below)

[b] Weighted effective dispensed cost, assuming public:private split of 25%:75%. These prices include the additional compound fee where compounding was undertaken at a TGA-licensed compounding site ($20).

[c] Undiscounted cost (sum of cells AH16:AH50, spreadsheet 'Model, Excel workbook 'Pembrolizumab Section 3 model November 2019').

[d] The discrepancy in the cost/patient/course for pembrolizumab between the model and the financial estimates was due to rounding of the number of cycles of treatment in the financial analysis.

[e] The difference in the cost for each regimen between the two sections is discussed below.

[f] Assuming equal proportions of total treated SOC patients receive each regimen.

6.69 The cost/patient/course of pembrolizumab derived using the truncated mean duration of treatment reported in KN170 ($[redacted]) will have underestimated the true mean cost/patient/course, as approximately 23% of patients were still on treatment at the April 2018 data cut-off (Table 10-1, p24 of KN170 Clinical Study Report).

6.70 The resubmission stated that the difference between the model and the financial estimates in the cost per patient per cycle for the comparator regimens was due to the fact that the model did not explicitly account for wastage or for hospital mark-ups at an individual patient level. The difference in the cost for each regimen between the two sections could not be fully reconciled during the evaluation. These differences had minimal impact on the overall outcome of the economic and financial analyses.

Estimated PBS usage & financial implications

6.71 This resubmission was not considered by DUSC. As in the previous submission, the resubmission presented an epidemiological approach to estimate the expected

utilisation and financial impact of listing pembrolizumab for the treatment of R/R PMBCL. In the absence of incidence data for PMBCL, the resubmission informed its estimates using Australian Institute of Health and Welfare data on nHL. This was reasonable.

6.72 The number of incident and prevalent patients with PMBCL was estimated assuming that PMBCL accounts for 2.5% of all incident nHL and 3% of the prevalent nHL population. The validity of these assumptions could not be assessed, as the original source of these estimates was not clear. The number of patients with R/R PMBCL who would be eligible for treatment with pembrolizumab was based on the treatment algorithm presented in the resubmission, with the proportion of patients qualifying at each step of the treatment pathways based on advice from 'key scientific leaders' (see Table 17). The resubmission did not provide any details regarding the 'key scientific leaders' nor how these inputs were derived. The PSCR argued that PMBCL is a very rare sub-type of non-Hodgkin lymphoma where there is a paucity of epidemiological data which would support a very accurate estimation of the treated patient population with pembrolizumab under the requested restriction.

Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident and prevalent nHL patients	Sourced from AIHW 2018 ACIM book for nHL	This source was appropriate.
Incident PMBCL patients	2.5% of incident nHL patients (Lees et al, 2019)	The validity of this input could not be assessed, as the primary source was not clear.
% incident patients who meet PBS criteria	Based on expert opinion Pathway 1: 90% respond 1L chemo, 20% relapse following 1L chemo/RT, 50% relapse after HDT-ASCT Pathway 2: 10% refractory to 1L chemo, 10% ineligible for ASCT Pathway 3: 10% refractory to 1L chemo, 90% eligible for 2L salvage + ASCT, 50% relapse after 2L salvage + ASCT	The eligible population was highly uncertain as the estimates were based on expert opinion (no further details were supplied).
Prevalent PMBCL population	3% of prevalent nHL patients. Source unclear.	The validity of this input was uncertain as it could not be verified.
% prevalent patients who meet PBS criteria (Year 1 only)	1.37%. As per the PBAC submission for classical Hodgkin's lymphoma (6.03 pembrolizumab COM, July 2017 PBAC meeting)[a]	The primary source for this input could not be located in the resubmission.
Grandfathered patients	Two patients in Year 1 of listing	These were in addition to the 9 prevalent patients in Year 1.
Uptake rate	95% for pembrolizumab (expert opinion) 90% for SOC	While uncertain, this seemed reasonable.
Dose/duration	Pembrolizumab: 200 mg/cycle, mean duration 16.1 cycles	This was consistent with the economic model.
Offsets for comparator	SOC doses based on eviQ regimens[b] Assumed equal proportions of total treated SOC patients receive each regimen. Assumed patients received either 2.5 cycles of ICE, 4 cycles of DHAP, or 4 cycles of GDP.	While these assumptions were the same as those in the model, the estimated cost per cycle for each regimen differed from those in the model (see Table 16). This had limited impact on the overall financial implications to the PBS/RPBS.
MBS items (IV administration)	Item 14245 (infusion immunomodulating agent >2 hrs)[c] Item 13918 (infusion cytotoxic chemo >1 hr but ≤ 6 hrs) Item 13921 (infusion cytotoxic chemo >6 hrs)	It may have been more appropriate to use MBS item 13915 for the IV infusion of pembrolizumab[c] The administration costs applied to the chemotherapy regimens were appropriate.

Source: Sections 4.2-4.4 of the resubmission; Excel workbook 'Pembrolizumab PMBCL BIM Nov 2019'.

1L = first line; chemo = chemotherapy; ACIM = Australian cancer incidence and mortality; AIHW = Australian Institute for Health and Welfare; ASCT = autologous stem cell transplantation; chemo = chemotherapy; DHAP = dexamethasone, high-dose cytarabine, cisplatin; GDP = gemcitabine, dexamethasone, cisplatin; HDT = high dose chemotherapy; hrs = hours; ICE= ifosfamide, carboplatin, etoposide; IV = intravenous; nHL = non-Hodgkin's lymphoma; PMBCL = primary mediastinal B-cell lymphoma; RT = radiotherapy; SOC = standard of care;

[a] The primary source of this data was Oncosight Patient Populations Hodgkin Lymphoma 2015-2025. This could not be located in the resubmission.

[b] Source: www.eviq.org.au

[c] As the product information for pembrolizumab recommends an IV infusion over 30 minutes, it may have been more appropriate to apply MBS item 13915 (IV administration cytotoxic chemotherapy ≤ 1 hour duration).

6.73 The number of scripts per patient (16.1 administrations per patient) and the cost per administration for pembrolizumab were the same as those in the economic model. As the mean duration of treatment (approximately 48 weeks) was less than one year, the resubmission's assumption that patients would receive the full course of therapy within one year was reasonable.

6.74 As discussed above, the cost per patient per course for DHAP, ICE and GDP differed from those used in the economic evaluation. This had minimal impact on the overall financial implications to the PBS/RPBS. Applying the average cost of SOC used in the economic model increased the estimated net cost to the PBS/RPBS over the first six years of listing from $10 million to < $20 million to $10 million to < $20 million.

6.75 The estimated use and financial implications of listing pembrolizumab for the requested indication are summarised in Table 18.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of pembrolizumab						
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for SOC (ICE, DHAP, GDP)						
Cost to PBS/RPBS less copayments	$105,850	$70,095	$71,717	$73,338	$74,959	$76,580
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Previous submission – November 2018						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Tables 4.2-20, 4.2-21, 4.2-22, p174-175 of the resubmission; Excel spreadsheet '5. Impact – net', Excel workbook 'Pembrolizumab PMBCL BIM Nov 2019'; Table 15, para 6.49, pembrolizumab rrPMBCL PBAC PSD, November 2018 PBAC meeting.
DHAP = dexamethasone, high-dose cytarabine, cisplatin; GDP = gemcitabine, dexamethasone, cisplatin; ICE= ifosfamide, carboplatin, etoposide; SOC = standard of care.
[a] Assuming 16.1 scripts per patient per year as estimated by the resubmission.

6.76 At Year 6, the estimated number of patients was less than 500 and the total cost to the PBS/RPBS of listing pembrolizumab was estimated to be $0 to < $10 million, with a total of $10 million to < $20 million in the first 6 years of listing, based on the proposed effective price for pembrolizumab. This compared to an estimated net cost of $0 to < $10 million in Year 6, with a total cost over 6 years of $10 million to < $20 million, in the previous submission.

6.77 The estimated net cost to the PBS/RPBS was lower than in the previous submission. This was primarily due to two factors: firstly, prevalent patients were only included in the first year of listing, whereas the previous submission assumed that prevalent patients would "drip-feed" into the treated patient group over the full six years of the analysis; and secondly, the proposed effective AEMP for pembrolizumab was reduced to $[redacted] per 100 mg vial from the previous proposed AEMP of $[redacted].

6.78 The net cost to the PBS/RPBS was highly uncertain, given the uncertainty in the incidence and prevalence of PMBCL, and the reliance on expert opinion to derive the

proportion of these patients who would be eligible for treatment with pembrolizumab under the requested restriction.

6.79 The resubmission assumed that there would be two grandfathered patients, in addition to prevalent patients, in the first year of listing. The pre-PBAC response stated the sponsor runs a cost-share program through which patients are able to access pembrolizumab and an estimated two patients are expected to be eligible under the proposed grandfathering clause. The PBAC considered that grandfathered patients would already be accounted for in the prevalent patient population in Year 1.

Quality Use of Medicines

6.80 The sponsor proposed the development of materials and a number of planned educational programs, including face to face workshops with health professionals and patients about how to identify and manage potential treatment-related adverse events with pembrolizumab. The resubmission also noted that a medical information service is available to respond to questions from patients, carers and health care professionals relating to these medicines.

Financial Management – Risk Sharing Arrangements

6.81 The resubmission indicated that the sponsor was willing to enter into a risk sharing arrangement (RSA). It proposed expenditure caps calculated to reflect the number of patients receiving pembrolizumab and the number of pembrolizumab cycles per patient as included in the base case economic model and financial analyses (i.e. 16.10 cycles per patient), and stated that the sponsor agreed to reimburse the Commonwealth with a considerable proportion of the treatment costs of pembrolizumab should use exceed the subsidisation cap in that year. The previous submission proposed two adjusted subsidisation caps, with the sponsor reimbursing [redacted]% of the treatment costs of pembrolizumab which exceed the first cap in that year, and [redacted]% of costs which exceed the second subsidisation cap, with the caps calculated on the basis of the annual pembrolizumab treated R/R PMBCL and R/R Hodgkin lymphoma patients and the average patient treatment cost ($[redacted]).

6.82 The sponsor proposed that the estimated R/R PMBCL treated population be added into the current R/R Hodgkin lymphoma RSA and Deed, with the current annual subsidisation caps in the R/R Hodgkin lymphoma RSA and Deed to be increased by an amount calculated on the basis of the annual pembrolizumab treated R/R PMBCL patients at the average R/R PMBCL patient treatment cost. The PSCR argued that there is precedent for sharing Deeds and RSAs across multiple indications, such as non-small-cell lung carcinoma.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of pembrolizumab, on the basis that it should be available only under special arrangements under Section 100 - Efficient Funding of Chemotherapy. The PBAC recommended the listing be made available for the treatment of relapsed or refractory primary mediastinal B-cell lymphoma (R/R PMBCL), under the circumstances shown in the table in Section 8 below.

7.2 The PBAC recognised the high clinical need for treatment options for this population and was satisfied that pembrolizumab showed effectiveness in the R/R PMBCL setting where patients may have no other potentially curative options available.

7.3 The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of pembrolizumab was uncertain but could be managed by a price reduction and subsidisation caps through a risk sharing arrangement (RSA).

7.4 The PBAC noted comments from consumers, health care professionals and organisations highlighting the impact of this rare disease on adolescents and young adults. The PBAC reiterated its November 2018 advice that there was a high unmet clinical need for effective treatments for P/R PMBCL, particularly given the poor outcomes in patients with this condition.

7.5 The PBAC agreed with the ESC that in clinical practice ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, high-dose cytarabine, cisplatin) or GDP (gemcitabine, dexamethasone, cisplatin) regimens would include the addition of rituximab and considered the inclusion of this agent in the resubmission appropriate for the comparator.

7.6 Acknowledging the limitations of the KN170 study (n=53), the PBAC noted that four additional R/R PMBCL patients were determined to have a complete response (18.9%) based on the 28 May 2019 data cut-off (median 22.3 months of follow-up) compared with the original 19 January 2018 data cut-off (median 9.7 months follow-up, 11.3% complete response). The PBAC also noted the ORR of 45.3% and the median OS of 22.3 months reported using the May 2019 data cut-off. The PBAC agreed with the ESC that pembrolizumab appears to show effectiveness. The PBAC acknowledged that more robust clinical trial data for pembrolizumab in this rare disease is unlikely to be forthcoming.

7.7 The PBAC noted the differences in transplant eligibility, prior lines of therapy and the proportion of patients pre-treated with rituximab-based therapy between the key studies used to inform the comparative effectiveness claim (KN170 and Vardhana 2018 – see paragraph 6.9). The PBAC considered that due to the differences in patient populations the effectiveness data from these two studies were not directly comparable. The PBAC also noted that the requested PBS population was broader than both the KN170 and Vardhana 2018 patient populations (see paragraph 6.10) and recalled that the Committee previously considered this reasonable given the

clinical need in this population.

7.8 The PBAC noted the evidence for the effectiveness of standard of care (SOC) was based on cohorts of patients in Vardhana 2018 and considered that the use of these cohorts meant that survival data informing SOC was based on a very small number of patients with a much lower OS rate than the full study population (18% for Cohort C versus 61% for the full study population at 3 years). The PBAC considered this approach likely underestimated the outcomes associated with current practice.

7.9 The PBAC considered that the claim of superior comparative effectiveness was uncertain but likely reasonable in the context of this rare sub-type of non-Hodgkin lymphoma with a low incidence.

7.10 The PBAC considered although the claim of superior comparative safety may be reasonable the magnitude of any benefit could not be quantified as there was no safety data presented in Vardhana 2018.

7.11 The PBAC noted that Cohort C from Vardhana 2018, which was used to represent the health outcomes of SOC in the base case of the economic model, consisted almost entirely of patients who were refractory to second line treatment, who had uniformly poor outcomes (see paragraph 7.8). The PBAC agreed with the ESC that the use of alternative Vardhana 2018 cohorts may have been more appropriate and considered that the sensitivity analyses provided in the resubmission did not allow assessment of the full extent of the uncertainty inherent in the choice of the cohort of patients. However, the PBAC considered that the use of alternative cohorts would not address the fact that the study population in KN170 represented a more treatment experienced population than that in Vardhana 2018, or that the survival outcomes in the two studies were determined from different time-points.

7.12 The PBAC noted the considerable uncertainties with the magnitude of the clinical benefit were further magnified by extrapolating the benefit over the 10-year time horizon in the model. The PBAC noted that reducing the time horizon of the model to 7.5 years increased the estimated ICER to $55,000 to < $75,000/QALY from a base case of $45,000 to < $55,000/QALY. The ICER further increased to $75,000 to < $95,000/QALY if the survival curves were converged over the period from 3 to 7.5 years. The PBAC considered the base case ICER to be highly uncertain and unacceptably high even in the context of a difficult to treat and relatively rare disease. The PBAC considered an ICER of $45,000 to < $55,000/QALY based on a model with a 7.5 year time horizon would be appropriate to ensure the drug is reasonably cost-effective.

7.13 The PBAC noted the use of advice from 'key scientific leaders' in the determination of the proportion of patients who would be eligible for treatment with pembrolizumab in the financial estimates. The PBAC noted that feedback from eight Australian haematologists estimated 15 patients per year would be eligible for treatment in Australia (see paragraph 6.3). The PBAC noted the financial estimates were uncertain

and a number of assumptions informing these estimates could not be assessed or verified during the evaluation process. As such, the PBAC considered the patient estimates should correspond with the estimated number of patients eligible for treatment provided by the eight Australian haematologists.

7.14 The PBAC recommended that a RSA would be appropriate to mitigate any residual uncertainties regarding the size of the eligible pembrolizumab population. The PBAC considered that a RSA separate to existing arrangements for R/R Hodgkin lymphoma would be appropriate for the R/R PMBCL population given they are two distinct patient populations. The PBAC advised the R/R PMBCL RSA should be based on the financial estimates with adjustments for the pembrolizumab price as outlined in paragraph 7.12 and number of treated patients as outlined in paragraph 7.13. The PBAC further advised a rebate of [redacted]% for use exceeding the financial caps would be appropriate.

7.15 The PBAC recommended a grandfather listing be in operation for 12 months to transition the small number of patients commenced on non-PBS subsidised treatment to PBS-subsidised treatment.

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

7.17 The PBAC recommended that the Early Supply Rule should not apply.

7.18 The PBAC found that the criteria prescribed by the National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for pembrolizumab:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over SOC. The PBAC considered this criteria was not met as the available data did not allow a reliable assessment of the magnitude of the incremental benefit;

b) The treatment is expected to address a high and urgent unmet clinical need; and

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

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

Outcome:

Recommended

8 Recommended listing

8.1 Add new indication:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
PEMBROLIZUMAB Injection	NEW (Public) NEW (Private)	200 mg	6	Merck Sharp and Dohme Pty Ltd
Available brands				
Keytruda (pembrolizumab 100 mg/4 mL injection, 4 mL vial)				

Category / Program: Section 100 – Efficient Funding of Chemotherapy

Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives

Restriction Level / Method: ☒ Authority Required – In Writing Only

Administrative Advice:
No increase in the maximum quantity or number of units may be authorised.
No increase in the maximum number of repeats may be authorised.
Special Pricing Arrangements apply.
Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.

Indication: Relapsed or refractory primary mediastinal B-Cell lymphoma

Treatment Phase: Initial treatment

Clinical criteria

- Patient must have refractory Primary Mediastinal B-cell Lymphoma following rituximab-based chemotherapy for this condition; OR
- Patient must have undergone an autologous stem cell transplant (ASCT) for this condition and have experienced relapsed or refractory disease post ASCT; OR
- Patient must not be suitable for ASCT for this condition and have experienced relapsed or refractory disease following at least 2 prior treatments for this condition, one of which must include rituximab with chemotherapy

  AND
- Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition

  AND
- The treatment must be the sole PBS-subsidised therapy for this condition

  AND
- The treatment must not exceed a total of 7 doses under this restriction

Prescribing Instructions:
Applications for authorisation of initial treatment must be in writing and must include:
(a) a completed authority prescription form;
(b) a completed primary mediastinal B-Cell lymphoma pembrolizumab PBS Authority Application, which includes:
(i) a declaration that PET and/or CT scans and histology results supporting a diagnosis of primary mediastinal B-Cell lymphoma have been retained on the patient's medical records;
(ii) a declaration of whether the patient's disease is relapsed or refractory, and the date and means by which the patient's disease was assessed as being relapsed or refractory.
(iii) dates of commencement and completion of 2 prior lines of treatment for patients not suitable for ASCT, one of which must include rituximab with chemotherapy.

Administrative Advice:
Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au

Applications for authority to prescribe should be forwarded to:
Department of Human Services
Complex Drugs
Reply Paid 9826
HOBART TAS 7001

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
PEMBROLIZUMAB Injection	NEW (Public) NEW (Private)	200 mg	6	Merck Sharp and Dohme Pty Ltd
Available brands				
Keytruda (pembrolizumab 100 mg/4 mL injection, 4 mL vial)				

Category / Program: Section 100 – Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☒ Authority Required – Telephone/Electronic/Emergency
Administrative Advice: No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply. Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.
Indication: Relapsed or refractory primary mediastinal B-Cell lymphoma
Treatment Phase: Continuing treatment
Clinical criteria:
▪ Patient must have previously received PBS-subsidised treatment with this drug for this condition
▪ **AND**
▪ Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition
▪ **AND**
▪ The treatment must not exceed a total of 35 cycles in a lifetime
Administrative Advice: Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Category / Program: Section 100 – Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☒ Authority Required – In Writing Only
Administrative Advice: No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply. Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.
Indication: Relapsed or refractory primary mediastinal B-Cell lymphoma **Treatment Phase:** Grandfather treatment (initial treatment of a patient commenced on non-PBS-subsidised treatment) **Clinical criteria:** ▪ Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [date of listing on the PBS] **AND** ▪ Patient must have refractory Primary Mediastinal B-cell Lymphoma following rituximab-based chemotherapy prior to initiating non-PBS-subsidised treatment with this drug for this condition; OR ▪ Patient must have undergone an autologous stem cell transplant (ASCT) for this condition and have experienced relapsed or refractory disease post ASCT prior to initiating non-PBS-subsidised treatment with this drug for this condition; OR ▪ Patient must not be suitable for ASCT for this condition and have experienced relapsed or refractory disease following at least 2 prior treatments for this condition, one of which must include rituximab with chemotherapy, prior to initiating non-PBS-subsidised treatment with this drug for this condition **AND** ▪ Patient must not have received treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition prior to initiating non-PBS-subsidised treatment with this drug for this condition **AND**

▪ Patient must not have developed disease progression while receiving treatment with this drug for this condition **AND** ▪ The treatment must not exceed a total of 35 cycles in a lifetime **AND** ▪ The treatment must not exceed a total of 7 doses of PBS-subsidised and non-PBS-subsidised supply combined under this restriction
Prescribing Instructions: Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; (b) a completed Primary Mediastinal B-Cell lymphoma pembrolizumab PBS Authority Application for Grandfathered patients, which includes: (i) a declaration that PET and/or CT scans and histology results supporting a diagnosis of primary mediastinal B-Cell lymphoma have been retained on the patient's medical records; (ii) a declaration of whether the patient's disease had relapsed or was refractory, and the date and means by which the patient's disease was assessed as being relapsed or refractory prior to initiating non-PBS subsidised treatment. (iii) dates of commencement and completion of 2 prior lines of treatment for patients not suitable for ASCT, one of which must include rituximab with chemotherapy;
Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria This grandfathering restriction will cease to operate 12 months after the date specified in the clinical criteria. Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001

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

9 Context for Decision

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

10 Sponsor's Comment

MSD is pleased with the outcome, since this will provide an additional treatment option for patients with this very rare cancer. MSD is working with the Department of Health to ensure that listing on the PBS occurs as soon as possible.