

6.03 PEMBROLIZUMAB, Powder for I.V. infusion, 50 mg and 100 mg vials, Keytruda[®], Merck, Sharp & Dohme (Australia) Pty Limited

1 Purpose of Application

- 1.1 The submission requested a Section 100 – Efficient Funding of Chemotherapy listing (private and public hospital) for pembrolizumab for the treatment of relapsed or refractory classical Hodgkin’s Lymphoma (rrcHL) in patients who have progressed following autologous stem cell transplant (ASCT), or who are ineligible for ASCT and have progressed on at least two prior systemic therapies.

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

| Component | Description |
|----------------|---|
| Population | Patients with relapsed or refractory classical Hodgkin's Lymphoma following autologous stem cell transplant (ASCT) failure, or Patients with relapsed or refractory classical Hodgkin's Lymphoma who are ineligible for ASCT due to age or co-morbidities and have progressed on at least two prior systemic therapies. |
| Intervention | Pembrolizumab 200mg intravenous every 3 weeks. |
| Comparator | Brentuximab vedotin (BV) 1.8mg/kg every 3 weeks as the main comparator. Gemcitabine/vinorelbine as a secondary comparator. |
| Outcomes | Quality of life (QoL), progression free survival (PFS), overall survival (OS) and safety. |
| Clinical claim | The submission claimed that, in classical Hodgkin's Lymphoma patients, who have relapsed or are refractory following ASCT, pembrolizumab is more effective than BV at improving progression free survival (PFS) and extending overall survival (OS), with an improved safety profile. |

Source: compiled during the evaluation from the submission

2 Requested listing

An abbreviated version of the requested restriction is below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics.

ASCT naïve:

| Name, Restriction, Manner of administration and form | Max. Amount | No.of Rpts | Dispensed price for maximum amount (DPMA) | Proprietary Name and Manufacturer |
|--|----------------|------------|---|---|
| PEMBROLIZUMAB 100mg vial for infusion, 1 | 200 mg | 5 | <i>To be confirmed</i> | Keytruda [®] Merck Sharp and Dohme Pty Ltd |

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| | |
|------------------------------------|---|
| Category / Program | Section 100 – Efficient Funding of Chemotherapy |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Treatment phase: | Initial treatment |
| Restriction Level / Method: | <input checked="" type="checkbox"/> Authority Required - In Writing |
| Clinical criteria: | <i>Patient must not have undergone an autologous stem cell transplant (ASCT) for this condition AND Patient must not be suitable for ASCT for this condition; OR Patient must not be suitable for treatment with multi-agent chemotherapy for this condition AND Patient must have experienced a relapsed CD30+ Hodgkin lymphoma following at least two prior treatments for this condition; OR Patient must have experienced a refractory CD30+ Hodgkin lymphoma following at least two prior treatments for this condition AND Patient must not have received prior treatment with a PD-1 inhibitor for this condition AND The treatment must be the sole PBS-subsidised therapy for this condition</i> |
| Prescriber Instructions | Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; (b) a completed Hodgkin lymphoma pembrolizumab PBS Authority Application; and (c) a signed patient acknowledgement form. |

| Name, Restriction, Manner of administration and form | Max. Amount | No. of Rpts | Dispensed price for maximum amount (DPMA) | Proprietary Name and Manufacturer |
|--|-------------|-------------|---|--|
| PEMBROLIZUMAB 100mg vial for infusion, 1 | 200 mg | 7 | To be confirmed | Keytruda® Merck Sharp and Dohme Pty Ltd |

| | |
|------------------------------------|---|
| Category / Program | Section 100 – Efficient Funding of Chemotherapy |
| Treatment phase: | Continuing treatment |
| Restriction Level / Method: | <input checked="" type="checkbox"/> Authority Required - Telephone |
| Clinical criteria: | <i>Patient must not have undergone an autologous stem cell transplant (ASCT) for this condition, AND Patient must not be suitable for ASCT for this condition; OR Patient must not be suitable for treatment with multi-agent chemotherapy for this condition, AND Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition.</i> |

Post ASCT:

| Name, Restriction, Manner of administration and form | Max. Amount | No. of Rpts | Dispensed price for maximum amount (DPMA) | Proprietary Name and Manufacturer |
|--|-------------|-------------|---|--|
| PEMBROLIZUMAB 100mg vial for infusion, 1 | 200 mg | 5 | <i>To be confirmed</i> | Keytruda® Merck Sharp and Dohme Pty Ltd |

| | |
|------------------------------------|--|
| Category / Program | Section 100 – Efficient Funding of Chemotherapy |
| Treatment phase: | Initial treatment |
| Restriction Level / Method: | <input checked="" type="checkbox"/> Authority Required - In Writing |
| Clinical criteria: | <p>Patient must have undergone a primary autologous stem cell transplant (ASCT) AND</p> <p>Patient must have experienced a relapsed CD30+ Hodgkin lymphoma post ASCT; OR</p> <p>Patient must have experienced a refractory CD30+ Hodgkin lymphoma post ASCT AND</p> <p>Patient must not have received prior treatment with a PD-1 inhibitor for this condition AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition</p> |
| Prescriber Instructions | <p>Applications for authorisation of initial treatment must be in writing and must include:</p> <p>(a) a completed authority prescription form;</p> <p>(b) a completed Hodgkin lymphoma pembrolizumab PBS Authority Application - <i>and</i></p> <p>(c) a signed patient acknowledgement form.</p> |

| Name, Restriction, Manner of administration and form | Max. Amount | No. of Rpts | Dispensed price for maximum amount (DPMA) | Proprietary Name and Manufacturer |
|--|-------------|-------------|---|--|
| PEMBROLIZUMAB 100mg vial for infusion, 1 | 200 mg | 7 | <i>To be confirmed</i> | Keytruda® Merck Sharp and Dohme Pty Ltd |

| | |
|------------------------------------|--|
| Category / Program | Section 100 – Efficient Funding of Chemotherapy |
| Treatment phase: | Continuing treatment |
| Restriction Level / Method: | <input checked="" type="checkbox"/> Authority Required - Telephone |
| Clinical criteria: | <p><i>Patient must have undergone an autologous stem cell transplant (ASCT) for this condition,</i> AND</p> <p><i>Patient must have previously received PBS-subsidised treatment with this drug for this condition</i> AND</p> <p><i>Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition.</i></p> |

- 2.1 The pre sub-committee response (PSCR) (p.2) agreed with the changes proposed by the Secretariat in order to align the requested listing for pembrolizumab with the

current listing of BV in the same patient population. The PBAC agreed this could be appropriate, but also considered that a single initial and a single continuing restriction would also be suitable.

- 2.2 The requested listing did not propose PD-L1 testing before targeting with pembrolizumab. The submission noted that gene amplification by 9p24.1 and less frequent chromosomal rearrangements lead to overexpression of PD-L1 and PD-L2 on Reed-Sternberg cells in patients with classical Hodgkin's lymphoma (cHL). In addition, Epstein Barr virus also increases PD-L1 expression in Epstein-Barr positive lymphomas. This provides a biological rationale for the use of an anti PD-1 agent without a requirement for PD-L1 testing since almost all patients will be PD-L1 positive. This argument appears to be consistent with evidence from the current literature¹. However, there is limited information provided in the submission on whether the strength of PD-L1 expression could be a treatment effect modifier for pembrolizumab (for example a specific cut off such as that proposed for NSCLC in past submissions). The ESC advised that the current literature did not have any substantial evidence to indicate that PD-1 expression was a treatment effect modifier in HL, largely because PD-1 is over-expressed in nearly all HL cases.
- 2.3 The submission was based on a cost-utility analysis of pembrolizumab compared with brentuximab vedotin (BV).
- 2.4 The recommended dose of pembrolizumab for the treatment of rrcHL is 200 mg administered as an intravenous infusion every three weeks. The draft Product Information indicated that treatment should be continued until disease progression or until a maximum of 35 treatment cycles.
- 2.5 The submission acknowledged that BV has an undisclosed [REDACTED] net price, and therefore the actual price for pembrolizumab would depend on the net price of BV for the proposed population.
- 2.6 The submission requested the listing of pembrolizumab via a Managed Entry Scheme (MES), and provided supporting information from currently available single-arm studies. The submission stated that the KEYNOTE (KN) 204 trial which directly compares pembrolizumab with BV in the proposed population will provide confirmatory evidence for the relative efficacy of pembrolizumab over BV and would

¹ Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *New England Journal of Medicine*. 2015; 372(4):311-9.

Carey CD, Connelly C, Gjini E, Roemer MG, Stack E, Hodi S, et al. Quantitative Assessment of PD-L1 Expression in Classical Hodgkin Lymphoma Suggests a Critical Role for Tumor Associated Macrophages in Suppressing Anti-Tumor Immunity. *Blood*. 2015;126(23):1440

Green MR, Monti S, Rodig SJ, Juszczynski P, Currie T, O'Donnell E, et al. Integrative analysis reveals selective 9p24. 1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2010;116(17):3268-77.

Moskowitz CH, Ribrag V, Michot J-M, Martinelli G, Zinzani PL, Gutierrez M, et al. PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: preliminary results from a phase 1b study (KEYNOTE-013). *Blood*. 2014;124(21):290

Tsirigotis P, Savani BN, Nagler A. Programmed death-1 immune checkpoint blockade in the treatment of hematological malignancies. *Annals of medicine*. 2016;48(6):428-39.

support a follow-up submission that is expected to be lodged in mid-2019. There are currently no preliminary data from the forthcoming KN204 randomised trial to enable any reasonable judgement on the comparative effectiveness and safety of pembrolizumab compared with BV for this indication. The Pre-PBAC response (p.2) subsequently withdrew this proposal for an MES.

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

3 Background

- 3.1 The submission was made under the TGA/PBAC Parallel Process. At the time of the PBAC consideration, the TGA Delegate's overview was not available to the Committee. The Clinical Evaluation Report (round 1) was received on 3 May 2017. The original TGA indication proposed by the sponsor was for the treatment of patients with refractory classical Hodgkin Lymphoma (cHL), or those who have relapsed after 3 or more prior lines of therapy". The clinical evaluation report recommended pembrolizumab be indicated as monotherapy for the treatment of adult patients with rrCHL following ASCT or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. This is consistent with the proposed population for whom listing of pembrolizumab is sought on the PBS. The Clinical Evaluation Report (round 2) was received on 31 May 2017 and included a suggested warning in line with that of the FDA for graft-versus-host-disease (GVHD) when use in patients undergoing allogeneic transplantation.
- 3.2 Pembrolizumab is currently TGA-registered for the treatment of unresectable or metastatic melanoma, metastatic or advanced non-small cell lung cancer (NSCLC), and recurrent or metastatic head and neck squamous cell carcinoma.
- 3.3 Pembrolizumab is currently PBS-subsidised for the treatment of unresectable Stage III or Stage IV malignant melanoma. This was the first submission to the PBAC for the treatment of rrCHL.

4 Population and disease

- 4.1 cHL is a cancer that is highly responsive to multi-agent first line chemotherapy and the disease is cured for the majority of patients. There is a small group of patients who either do not respond or relapse following initial chemotherapy. Some of these patients have a chance of a cure with high dose chemotherapy followed by ASCT, but some are not eligible for ASCT. About 50% of patients relapse following ASCT. In the submission, the proposed population for treatment with pembrolizumab are those patients who have refractory or relapsed disease following ASCT, and those who are ineligible for ASCT.

5 Comparator

- 5.1 The submission nominated BV as the main comparator. This is the appropriate comparator for patients who have not been treated with BV previously.
- 5.2 The requested restriction did not specifically exclude patients who had prior exposure to BV. For these patients, chemotherapy use (post BV) would be the relevant comparator. The submission did not compare pembrolizumab with salvage chemotherapy post BV in patients with rrcHL.
- 5.3 The ESC considered that it was highly likely that a large number of patients would receive BV prior to pembrolizumab when pembrolizumab is first made available in Australia due to the timing of the clinical trials for BV ahead of pembrolizumab, and the current PBS listing of BV as salvage therapy in the relapsed or refractory setting.
- 5.4 The current listing for BV would allow for BV to be used following progression on pembrolizumab. Should pembrolizumab for rrcHL be recommended, it is likely that some BV would be displaced, rather than replaced, to a later line of therapy following pembrolizumab-failure in clinical practice. This would have substantial economic and financial implications. The ESC agreed that, over time, the PBS listing of pembrolizumab would displace, rather than replace, BV for the majority of patients. Further, the ESC noted that the clinical algorithm for HL was rapidly evolving, and considered that currently there was insufficient evidence to determine the order in which pembrolizumab and BV would be prescribed in future clinical practice. The Pre-PBAC response (p.1) acknowledged that there was no evidence to dictate the order of treatment at present, nor are any trials currently underway that could inform the appropriate order of treatment in the near future, but contended that this was not unexpected, given the rarity of the condition.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. At the hearing, a haematologist presented clinical case studies to support the effectiveness of pembrolizumab in both post ASCR and ASCT naïve settings. The haematologist discussed promising results with nivolumab, a pharmacological analogue of pembrolizumab, in patients with rrcHL, to further support the claimed effectiveness of pembrolizumab. The haematologist indicated that pembrolizumab and BV were likely to be sequentially prescribed in practice in later line settings, and addressed other matters in response to the Committee's questions. The optimal sequencing of BV and pembrolizumab would be assessed based on the clinician's assessment of each individual's circumstances. The PBAC considered that the hearing was informative as it provided

a clinical perspective on the potential use of pembrolizumab for rrcHL in the Australian clinical setting.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (125), health professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments highlighted the tolerability of pembrolizumab in heavily pre-treated patients compared to chemotherapy, and discussed its effects in improving quality of life and slowing disease progression.
- 6.3 The PBAC noted advice from Lymphoma Australia advocating that pembrolizumab is well tolerated and provides an improved quality of life to patients with rrcHL. The PBAC also noted Rare Cancer Australia's support for PBS listing of pembrolizumab. The PBAC noted that this advice was supportive of the evidence presented in the submission.

Clinical trials

- 6.4 The submission was based on data sourced from two single-arm pembrolizumab studies, one single-arm BV study and one retrospective salvage chemotherapy study.

Pembrolizumab studies:

KN087 multi-cohort study (N=210):

- Cohort 1 (N=69): rrcHL patients who had failed to achieve a response to any line of chemotherapy (including BV) or who had relapsed after ASCT and BV;
- Cohort 2 (N=81): rrcHL patients who had failed salvage chemotherapy and were ineligible for ASCT and had failed BV therapy; and
- Cohort 3 (N=60): rrcHL patients who had failed to achieve a response to any line of chemotherapy or progressed after ASCT and had not received BV post ASCT. These subjects could have received BV as part of primary or salvage treatment (25/60 or 40% of Cohort 3 had received BV).

KN013: One single-arm study (Cohort 3; N=31) included patients with rrcHL who had failed, were ineligible for or had refused a stem cell transplant (SCT). 9/31 (29%) were ineligible for or naïve to ASCT. Patients in this cohort had to have been treated with or failed to respond to BV.

Only 35 (of a total 210) patients in KN087 and 0 of 31 patients in KN013 received pembrolizumab without having previously received BV.

Brentuximab study:

Study 0003 (N=102) was a single-arm study of BV in rrcHL patients after high-dose chemotherapy and ASCT (post ASCT). Patients had to have histologically documented CD30-positive Hodgkin's Reed-Sternberg cells. However, the evidence

for BV considered by the PBAC in 2016 was different from that presented in the current submission:

- For the post ASCT population, although Study 0003 was also considered in 2016 by the PBAC, only data from a subgroup of 1st line post ASCT patients in 0003 were presented (n=45). These data were supplemented by unpublished data from the AETHERA study for placebo arm patients who, during long term follow-up, received BV 1st line post ASCT); and
- For the ASCT ineligible/naïve population, the PBAC considered several BV studies in November 2016. No BV evidence in this population was presented in this submission.

Salvage chemotherapy (gemcitabine plus vinorelbine) study:

Czyz et al, 2013 (N=37) was a retrospective study of two gemcitabine based therapies in patients with cHL who had relapsed or progressed after receiving ASCT. The intention of treatment was to reduce tumour burden in order to proceed to either an allogeneic SCT or a second ASCT.

6.5 Details of the studies presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

| Trial ID/First Author | Protocol title/ Publication title | Publication citation |
|---|--|--|
| Pembrolizumab (single-arm studies) | | |
| KN087 | A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL) P087V01. <u>Abstracts</u> Chen <i>et al.</i> Phase II study of pembrolizumab (MK-3475) for relapsed/refractory classical Hodgkin Lymphoma (r/r cHL): Keynote-087. Chen <i>et al.</i> Pembrolizumab for relapsed/refractory classical Hodgkin lymphoma (R/R cHL): phase 2 KEYNOTE-087 study. | <i>Journal for ImmunoTherapy of Cancer</i> 2015; 3 (Supplement 2).p146. <i>Journal of Clinical Oncology</i> 2016; 34ASCO Abstract 7555. |
| KN013 | A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Hematologic Malignancies. P013V01. <u>Publication</u> Armand <i>et al.</i> Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. <u>Abstracts</u> Moskowitz <i>et al.</i> PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: Preliminary results from a phase 1B study (KEYNOTE-013). | <i>Journal of Clinical Oncology</i> 2016; 34(31): 3733-3739. <i>Blood</i> 2014; 124 (21). |

| Trial ID/First Author | Protocol title/ Publication title | Publication citation |
|---|---|--|
| | <p>PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: Preliminary results from a phase Ib study (KEYNOTE-013).</p> <p>Armand <i>et al.</i> PD-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: Safety, efficacy, and biomarker assessment.</p> <p>Kline <i>et al.</i> KEYNOTE-013: An open-label, multicohort phase Ib trial of pembrolizumab in patients with advanced hematologic malignancies.</p> | <p><i>Clinical Advances in Hematology and Oncology</i> 2015; 13 (Supplement 2).</p> <p><i>Blood</i> 2015; 126 (23).</p> <p><i>Journal for ImmunoTherapy of Cancer</i> 2016; 4 (Supplement 1).</p> |
| Brentuximab vedotin (single-arm study) | | |
| Study 0003 | <p><u>Publications</u></p> <p>Younes A, Gopal AK, Smith SE, <i>et al.</i> Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma.</p> <p>Gopal <i>et al.</i> Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma.</p> <p>Chen <i>et al.</i> Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma.</p> <p><u>Abstracts:</u></p> <p>Chen <i>et al.</i> Results of a pivotal phase 2 study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma.</p> <p>Younes <i>et al.</i> Durable complete remissions in a pivotal phase 2 study of SGN-35 (brentuximab vedotin) in patients with relapsed or refractory Hodgkin lymphoma (HL).</p> <p>Fanale <i>et al.</i> Retrospective analysis of the safety and efficacy of brentuximab vedotin in patients aged 60 years or older with relapsed or refractory CD30+ hematologic malignancies.</p> <p>Chen <i>et al.</i> Long-term survival analyses of an ongoing phase 2 study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma.</p> <p>Karuturi <i>et al.</i> Overall survival benefit for patients with relapsed Hodgkin lymphoma treated with brentuximab vedotin after</p> | <p><i>Journal of Clinical Oncology</i> 2012; 30(18): 2183-2189.</p> <p><i>Blood</i> 2015; 125 (8):1236-1243</p> <p><i>Blood</i> 2016; 128 (12):1562-1566</p> <p><i>Journal of Clinical Oncology</i> 2011; 29: (ASCO Abstract 8031)</p> <p><i>Annals of Oncology</i> 2011; 22 (Supplement 4).</p> <p><i>Blood</i> 2012; 120 (21): p3687</p> <p><i>Blood</i> 2012; 120 (21): p3689</p> <p><i>Blood</i> 2012; 120 (21): p3701</p> |

| Trial ID/First Author | Protocol title/ Publication title | Publication citation |
|--|--|--|
| | <p>autologous stem cell transplant.</p> <p>Chen <i>et al.</i> Three-year follow-up data and characterization of long-term remissions from an ongoing phase 2 study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma.</p> <p>Smith <i>et al.</i> Long-term follow-up results of an ongoing pivotal study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma (HL).</p> <p>Younes <i>et al.</i> Durable complete remissions in a pivotal phase 2 study of SGN-35 (brentuximab vedotin) in patients with relapsed or refractory Hodgkin lymphoma (HL).</p> <p>Chen <i>et al.</i> Five-year survival data demonstrating durable responses from a pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma.</p> | <p><i>Blood</i> 2013; 122 (21). p4382.</p> <p><i>Haematologica</i> 2012; 97 (Supplement 1).</p> <p><i>Journal of Cancer Research and Clinical Oncology</i> 2012; 138 (Supplement 1).</p> <p><i>Blood</i> 2015; 126 (23).</p> |
| Salvage chemotherapy with gemcitabine plus vinorelbine (retrospective single-arm study) | | |
| Czyz, 2013 | <p><u>Publication</u></p> <p>Czyz <i>et al.</i> Treatment strategy based on gemcitabine-containing salvage chemotherapy used with intent to proceed to second stem cell transplant for patients with Hodgkin lymphoma relapsing after a prior autologous transplant.</p> | <p><i>Leukemia and Lymphoma</i> 2013; 54(5):973-978.</p> |

Pembrolizumab report dates were not provided in the submission.

Source: Table 2A.2-1, p30 of the submission

6.6 The key features of the single-arm studies for pembrolizumab, BV, and chemotherapy are summarised in the table below.

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

| Study | n used | Design/ median follow-up or study period | Risk of bias | Patient population | Outcomes | Used in modelled evaluation? |
|---|-----------------------------|--|--------------|---|--------------|--|
| Pembrolizumab | | | | | | |
| KN087 Cohort 1: Cohort 2: Cohort 3: | (ITT=210) 69 81 60 | Multi-cohort single-arm study of pembrolizumab (200mg Q3W) Median follow-up 10.1 months, (range:1-15). (200mg Q3W is consistent with draft PI.) | High | rrcHL (Post ASCT and ASCT naïve) Predominantly after BV failure Cohort 1: Cohort 2: Cohort 3: | OS, PFS, ORR | No |
| KN013 | ITT=31 | Single-arm study of pembrolizumab (10mg/kg every two weeks) Median follow-up 24.9 months, (range: 7-29.7). (10mg/kg Q2W is not consistent with draft PI.) | High | rrcHL (Post ASCT and ASCT naïve) after BV failure | OS, PFS, ORR | No |
| BV | | | | | | |
| Study 0003 | ITT:102 | Single-arm study of BV Latest median follow-up: 35.1 months ⁴ | High | rrcHL post ASCT, any line (ITT). BV naïve | OS, PFS, ORR | Yes ITT, post-ASCT any line (n=102) included as comparator outcome data. (Hypothesised HRs for pembrolizumab from KN204 trial applied to estimate pembrolizumab outcomes.) |
| Salvage chemotherapy (gemcitabine + vinorelbine) | | | | | | |
| Czyz 2013 | ITT: 37 | Retrospective analysis | High | rrcHL post ASCT, any line ⁵ | OS, PFS, ORR | No |

¹Cohort 1 (N = 69)–ASCT experienced: Failed to achieve a response or progressed after ASCT. Subjects must have relapsed after treatment with or failed to respond to BV post ASCT.

²Cohort 2 (N=81)–ASCT naïve: Were unable to achieve a CR or a PR to salvage chemotherapy and did not receive ASCT. Subjects must have relapsed after treatment with or failed to respond to BV. 76/81 (94%) were considered ineligible for ASCT on the basis of chemo-resistance to salvage treatment.

³Cohort 3 (N=60)–ASCT experienced: Failed to achieve a response or progressed after ASCT and had not received BV post ASCT. Subjects who may have received BV as part of their primary treatment, or as part of salvage treatment prior to ASCT, were included (n/N=25/60).

⁴From most updated data in Chen et al 2016^[1].

⁵Prior to gemcitabine-based chemotherapy, eight of the 37 post-transplant relapsed patients had received an alternative salvage regimen including either ifosfamide, etoposide or high dose cytarabine.

ASCT = autologous stem cell transplant; BV = brentuximab vedotin; rrcHL = relapsed or refractory classical Hodgkin's lymphoma; ITT = intention-to-treat; ORR = overall response rate; OS=overall survival; PFS=progression-free survival; ORR = objective response rate; Q3W = every three weeks; Q2W = every two weeks.

Source: compiled during the evaluation

[1] Chen R, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2016:blood-2016-02-699850

- 6.7 The majority of patients enrolled in the pembrolizumab single-arm studies were BV experienced, and thus represented rrcHL patients who had been treated with later-line therapies. This differed from the patients in the BV or chemotherapy studies. These studies do not represent patients in the same treatment setting, and so cannot be indirectly compared because of the transitivity concerns.
- 6.8 Eligibility for the BV and salvage chemotherapy studies was restricted to patients who had failed ASCT whereas 30% to 40% of patients enrolled into the pembrolizumab studies were ASCT ineligible due to chemo-insensitivity. No BV studies on ASCT naïve patients were included in the submission.
- 6.9 The submission stated that the forthcoming “confirmatory” data from KN204 represented patients with rrcHL who had no previous treatment with BV, and either 1) had failed to achieve a response to, or progressed after, ASCT, or 2) are not ASCT candidates and have received at least 2 prior multi-agent chemotherapy regimens. The eligibility criteria for the direct KN204 trial appear relevant and applicable to the population for whom listing of pembrolizumab on the PBS is being sought.
- 6.10 Overall, the included evidence was associated with considerable uncertainty arising from the comparisons across single-arm studies, and the inability to conduct formal statistical comparisons between studies due to important transitivity issues. The ESC agreed, noting that the evidence presented in the submission included limited data on response in BV-naïve patients, and that this will be addressed with the KN204 trial.

Comparative effectiveness

- 6.11 The key effectiveness data from KN087 study are presented below. The OS data remain immature and the median OS was not reached. The OS rate at 12 months was close to 100% in KN087 (median follow up duration of approximately 10 months). In the KN013 study patients were treated with a weight dependent dose regimen of 10mg/kg of pembrolizumab, which was inconsistent with the fixed dose regimen of 200mg proposed in the draft product information (and therefore the results of this study were not presented). The line of treatment differed between KN087 and Study 0003 except for the small subset of cohort 3 of KN087 (16% of study KN087). OS data for this cohort were not reported and median OS for all three cohorts in KN087 has not yet been reached.

Table 4: Key effectiveness results from KN087 (single-arm study of pembrolizumab 200mg, every three weeks).

| Outcome | All patients (N=210) | Cohort 1 Received BV post ASCT (N=69) | Cohort 2 ASCT ineligible; Received BV (N=81) | Cohort 3 Did not receive BV post ASCT [some patients received BV prior to ASCT 25/60] (N=60) |
|--------------------------------|-------------------------|--|---|---|
| ORR n (%) [95% CI] | | | | |
| CRR n (%) [95% CI] | | | | |
| Median DOR, months [95% CI] | | | | |
| Median PFS, months [95% CI] | | | | |
| PFS rate at 9 months (%) | | | | |
| PFS rate at 12 months (%) | | | | |
| Median OS, months [95% CI] | | | | |
| OS rate at 12 months (%) | | | | |

Data cut-off date September 2016. Median duration of follow up: 10.1 months (Range 1.0 to 15.0 months)

Response data based on Central Independent Review

CRR = complete response rate; ORR = objective response rate; DOR = duration of response; NE = not estimable (not reached); OS = overall survival; PFS = progression free survival; TTR = time to response; BV = brentuximab vedotin; ASCT = autologous stem-cell transplants.

Source: Table 2A.5-9, p68 of the main submission.

6.12 The key results from Study 0003 are summarised below.

Table 5: Study 0003 - Key effectiveness results from Study 0003 (single-arm study of brentuximab vedotin 1.8mg/kg)

| Outcome | All patients (N=102) | | |
|----------------------------|---|--|---|
| | n (%) | [95% CI] | |
| CRR | 35 (34) | [24.3, 43.4] | |
| PR | 41 (40) | Not reported | |
| Objective Response (CR+PR) | 76 (75) | [64.9, 82.6] | |
| Stable Disease (SD) | 22 (22) | Not reported | |
| Progressive Disease (PD) | 3 (3) | Not reported | |
| | Median follow up 18.5 months (Younes 2012) | Median follow up 33.3 months (Gopal 2015)² | Median follow up 35.1 months (Chen 2016)² |
| Median OS [95% CI] | 22.4 [21.7, NE] ¹ | 40.5 [28.7, NE] | 40.5 [28.7, 61.9] |
| OS rate | At 12 months 89% | At 3 years 47% | At 5 years 41% |
| Median PFS [95% CI] | 5.6 [5.0, 9.0] | 9.3 [7.1, 12.2] | 9.3 [7.1, 12.2] |

¹Sourced from Younes 2012.

²3 year and 5 year follow up OS data sourced from Gopal (2015) and Chen (2016).

CRR = complete response rate; ORR = objective response rate (CR+PR); NE = not estimable (not reached); OS = overall survival; PFS = progression free survival.

Sources: Younes (2012), Gopal (2015), Chen (2016) and Section 2A of the main submission

- 6.13 Data for salvage chemotherapy from Czyz 2013 were not used in the economic evaluation. In Czyz 2013, patients had failed ASCT and the publication did not discuss whether patients were also previously exposed to BV before enrolment.
- For a median follow-up time among surviving patients of 26.4 months, the 2-year and 3-year OS rates for all patients were 36% (95% CI: 19%, 53%) and 30% (95% CI: 13%, 48%), respectively;
 - Median OS and PFS times were 17 months and 8 months, respectively (confidence interval not reported). The estimated 2-year PFS rate was 25% (95% CI: 11%, 40%); and
 - Complete response rate and objective response rate were approximately 10% and 60%, respectively. The combination of gemcitabine, cisplatin, and steroid appeared to be associated with higher response rates compared with gemcitabine plus vinorelbine.
- 6.14 In addition to the immaturity of the clinical evidence presented and the inherent bias of the comparisons across single-arm studies, the ESC considered that the claim of clinical superiority was not supported by the response outcomes in the naïve indirect comparison (CR 24% vs 34% (KN087 vs 0003); ORR 69% vs 75% (KN087 vs 003)) and OS data for pembrolizumab was immature (OS at 12 months 97.6% vs 89% (KN087 vs 0003)). The ESC further considered that, although an ORR of 69% in patients with relapsed, refractory disease was promising in a population most of whom were pre-treated with BV, the comparative effectiveness of pembrolizumab was difficult to determine.

Comparative harms

- 6.15 In the pembrolizumab study KN087, the majority of patients experienced an adverse event (AE) with nearly 75% of these events being considered to be related to pembrolizumab. The frequency of serious AEs was approximately 16% with a slightly lower rate (11%) of Grade ≥ 3 AEs. Grade 3-5 myocarditis was approximately 3% in Cohort 1 but only 1% in the whole KN087 population. Other immune-mediated AEs occurred with low frequencies. Nine patients (9/210 = 4.3%) discontinued as a result of a drug-related AE. The most common reason for discontinuation was pneumonitis, which lead to treatment discontinuation in 4 of the 6 affected patients. Hypothyroidism was the most common AE, occurring in approximately 17% of patients in Cohort 3 and 12% of patients across all cohorts.
- 6.16 The ESC advised that these AEs were not uncommon in this clinical setting and the clinical need should be considered from this perspective.

Table 6: KN087 – Pembrolizumab 200mg fixed dose AE summary by cohort (ASaT population)

| | COHORT 1 | | COHORT 2 | | COHORT 3 | | Total | |
|---|----------|-----|----------|-----|----------|-----|-------|-----|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Subjects in population | 69 | | 81 | | 60 | | 210 | |
| with one or more AEs | | | | | | | | |
| with drug-related† AEs | | | | | | | | |
| with toxicity grade 3-5 drug-related AEs | | | | | | | | |
| with serious AEs | | | | | | | | |
| with serious drug-related AEs | | | | | | | | |
| who died | | | | | | | | |
| who died due to a drug-related AE | | | | | | | | |
| discontinued due to a drug-related AE | | | | | | | | |
| discontinued due to a serious drug-related AE | | | | | | | | |

(Database Cutoff Date: 25SEP2016).

† Determined by the investigator to be related to the drug.

‡ Study medication withdrawn.

Grades are based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

AEs = Adverse events. ASaT = All subjects as treated.

Non-serious AEs up to 30 days of last dose and serious AEs up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Source: Table 2A.5-13, p77 of the main submission.

- 6.17 In the BV Study 0003, 14% and 6% of patients experienced Grade 3 and Grade 4 neutropenia, respectively. Additionally, 8% of patients had a Grade 3 peripheral neuropathy (PN).
- 6.18 In the salvage chemotherapy study Czyz 2013, the most frequent AEs were Grade 3-4 neutropenia/thrombocytopenia. The proportions of patients with Grade 3-4 neutropenia, thrombocytopenia and anaemia were 41%, 35% and 35%, respectively.
- 6.19 The immaturity of the data from the KN087 study made it difficult to draw any conclusions regarding absolute longer-term safety. In addition, a meaningful comparison of safety between pembrolizumab, BV, and salvage chemotherapy was difficult to undertake, given the comparisons across single-arm studies and differences across the studies in terms of treatment lines, ASCT status and other patient characteristics.
- 6.20 The ESC noted that the proposed listing did not exclude patients who have had an allogeneic bone marrow transplantation, a procedure that would be a clinical consideration in a significant proportion of relapsed / refractory patients with HL. A recent publication² indicated that the immune effects of PD-1 inhibition increase the risk of fatal GVHD in patients who have undergone an allograft. Other studies reported that reactivation was not observed. The ESC noted that the TGA Clinical Evaluation Report (round 2) for pembrolizumab also stated that more data were required to understand the contribution of pembrolizumab in the development of GVHD in patients receiving allogeneic bone marrow transplantation. The Pre-PBAC

² Singh A.K. et al 'Fatal GvHD induced by PD-1 inhibitor pembrolizumab in a patient with Hodgkin's lymphoma' *Bone Marrow Transplantation* (2016) 51, 1268–1270; doi:10.1038/bmt.2016.111;

Bradley M. et al. 'Checkpoint Blockade for Treatment of Relapsed Lymphoma Following Allogeneic Hematopoietic Cell Transplant: Use May be Complicated By Onset of Severe Acute Graft Versus Host Disease' *Blood* 2016 128:1163;

Bruce R. et al. 'Blockade of Programmed Death-1 Engagement Accelerates Graft-Versus-Host Disease Lethality by an IFN- γ -Dependent Mechanism' *J Immunol* August 1, 2003, 171 (3) 1272-1277

response (p.1) stated that the Product Information of pembrolizumab will include a statement noting that close monitoring for early evidence of transplant-related complications is recommended. The Pre-PBAC response (p.1) further proposed that if deemed appropriate, a similar statement could be included as a 'note' to the PBS restriction. The PBAC considered that, given the very small number of allografts for HD, it would be appropriate to leave this matter in the hands of the specialists rather than adding notes to the PBS listing.

Benefits and harms

- 6.21 The naïve indirect comparison presented in the submission did not allow for a meaningful comparison of the benefits and harms between pembrolizumab and either BV or salvage chemotherapy. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.22 For the naïve indirect comparison of pembrolizumab and BV from Studies KN087 and 0003 respectively, the therapeutic claim made in the submission was that pembrolizumab provides superior clinical benefit in terms of PFS and OS compared to BV, and superior safety in terms of severe Grade 3 or Grade 4 AEs.
- 6.23 For the comparison of pembrolizumab with gemcitabine plus vinorelbine, the therapeutic claim made in the submission was since BV was shown to be superior to this combination (Brentuximab vedotin (Post-ASCT) Public Summary Document, November 2016), by extension, pembrolizumab also provides superior effectiveness compared with gemcitabine plus vinorelbine.
- 6.24 The ESC considered that the therapeutic conclusion presented in the submission was not adequately supported by the evidence presented in the submission:
- The evidence was based on non-transitive comparisons across single-arm studies with no common comparator to enable a formal adjusted indirect statistical analysis.
 - The included studies represent non-comparable populations, therefore they did not enable any reasonable naïve comparison to inform the proposed treatment line where pembrolizumab is expected to replace BV. The evidence presented in the submission was primarily based on patients who had failed BV, whether in patients post ASCT or who were ASCT ineligible.
 - Comparative BV data were not provided for the ASCT ineligible population, thereby making it difficult to evaluate pembrolizumab's comparative effectiveness in this population.
 - No preliminary data from the forthcoming KN204 randomised trial were available at the time of evaluation to enable any reasonable judgement on comparative effectiveness and safety in the populations and line of therapy for which BV is currently listed.

- 6.25 Overall, magnitude and direction of the comparative benefit and harm was difficult to determine from the data provided.
- 6.26 The submission acknowledged there are uncertainties with the superiority claim due to the nature of the currently available evidence and that these uncertainties would be resolved as data from KN204 become available (refer to “Managed Entry Scheme/Managed Access Programme” section below).
- 6.27 The Pre-PBAC response (p.1) acknowledged the concerns raised by ESC regarding the inadequacy of the evidence to support the submission’s claim of superiority, and proposed to vary the clinical claim to one of non-inferiority against BV, on the basis of OS data from single-arm studies.
- 6.28 The PBAC noted the amended claim of non-inferiority put forth in the Pre-PBAC response, and considered that cost-minimisation to BV could be an appropriate way forward in recommending pembrolizumab for PBS listing.

For more detail on PBAC’s view, see section 7 “PBAC outcome.”

Economic analysis

- 6.29 The type of economic evaluation presented in the submission was a threshold analysis (ICER limit of \$45,000/QALY - \$75,000/QALY) based on a hypothetical cost-utility analysis of pembrolizumab versus BV in patients with rrcHL. The submission did not use the effectiveness data for pembrolizumab reported in KN087 and KN013 studies in the economic evaluation. Pembrolizumab survival curves in the economic evaluation were estimated using the hazard ratios (HRs) used for the power calculations of KN204 trial (0.600 for OS and 0.622 for PFS), and applied to the BV survival data reported in Study 0003. The rationale for the selection of the assumed HRs used in these power calculations was not provided in the KN204 trial protocol.
- 6.30 The PSCR (p.3) contended that the KN087 data closely matched the modelled pembrolizumab survival curves, and claimed that the use of KN087 Kaplan-Meier curves for the first 12 to 15 months of follow-up would yield similar results. However, the ESC considered that this issue was not adequately addressed in the PSCR. The available 1-year data from KN087 were not mature enough to predict the final shape of the pembrolizumab survival curves. In addition, the modelled pembrolizumab PFS estimates were more optimistic than the KN087 data within the first year of the time horizon. Further, the ESC noted that, in the economic model, the death rate in the pembrolizumab arm at 12 months was higher than in study KN087 (97% still alive vs 89% still alive in BV arm [Study 003]). As such, the ESC considered that it was unlikely that the assumed HRs were an appropriate representation of the clinical evidence.

6.31 Table 7 below summarises the key components of the economic evaluation.

Table 7: Summary of model structure and rationale

| Component | Description | Rationale/comments |
|----------------------------------|---|---|
| Type of analysis | Cost-utility analysis | This would be reasonable if the superiority clinical claim (pembrolizumab vs BV) was acceptable. |
| Outcomes | Quality-adjusted life years, life years | These are appropriate health outcomes for a cost-utility analysis. |
| Time horizon | 8 years in the base case of the model (vs expected median follow-up of 2 years in the key trial of KN204) Sensitivity analyses: time horizons of 5 years and 10 years. | An 8-year time horizon was considered appropriate by the PBAC when the Committee considered the BV submission at the March 2015 PBAC meeting. |
| Methods used to generate results | Cohort expected value, partitioned survival analysis (i.e. area under the curve) | This is reasonable. |
| Health states | Progression-free, progressive disease and death | This is reasonable. |
| Cycle length | 3 weeks | This is appropriate and consistent with the treatment cycle for both pembrolizumab and BV. Note, the model incorrectly used a cycle length of 1 month in calculating the accumulative costs and/or health outcomes over the model time horizon. Results were corrected during the evaluation (see Table 9). |
| Utilities | Utility values applied to the PFS and PD health states in the base case economic model were sourced from the EQ-5D utility scores measured at Week 12 in Study KN087. | KN087 subjects may be more heavily pre-treated than the proposed PBS population and the majority of patients had received BV before enrolment. Therefore, the EQ-5D utility values observed from KN087 study may not be applicable to the proposed PBS population. In addition, EQ-5D utility scores measured at a single time point of the study from a small number of patients before and after disease progression may not represent the overall utility weights for patients in the PFS and progressive health states, respectively. |

| Component | Description | Rationale/comments |
|------------------------|---|--|
| Transition probability | <p>PFS and OS data were the basis for determining the proportions of patients remaining in the PFS health state and death health state, respectively, per cycle. The proportion of patients in the progressive disease state was assumed to be the difference between OS and PFS. The PFS and OS estimates were determined by:</p> <ul style="list-style-type: none"> • Pembrolizumab arm: applying assumed HRs to PFS and OS estimates from the BV 0003 study for the first 2 years. Then the pembrolizumab survival curves converged towards the BV curves from Year 3 to Year 8. • BV arm: using 5-year survival data from Study 0003. The survival curves were extrapolated to the 8-year time horizon using parametric survival functions. | <p>The use of an assumed comparative treatment effect of pembrolizumab relative to BV is the main economic uncertainty. In addition, it is unknown whether the BV survival estimates reported in Study 0003 are applicable to the Australian target population, as this study did not recruit a proportion of patients who were ineligible for ASCT.</p> |

ASCT = autologous stem cell transplantation; BV = brentuximab vedotin; OS = overall survival; PD = progressive disease; PFS = progression-free survival

Source: Table 3A.1.1, p106 of the submission

6.32 The key drivers of the model are summarised in Table 8 below.

Table 8: Key drivers of the model

| Description | Method/Value | Impact |
|--|--|--------------------------------------|
| Drug costs for BV (including the price of BV and the number of cycles of BV) | <p>Published BV price was used in the model</p> <p>The number of BV cycles was estimated by assuming that patients would receive BV for a maximum number of cycles (16) unless they experienced disease progression (determined on the basis of the PFS curve in Study 0003) earlier</p> | High, favours BV |
| Hazard ratio of PFS for pembrolizumab over BV | Assumed to be 0.622 as used in the power calculations in the trial KN204 protocol | High, likely to favour pembrolizumab |
| Hazard ratio of OS for pembrolizumab over BV | Assumed to be 0.6 as used in the power calculations in the trial KN204 protocol | High, uncertain |
| The number of treatment cycles for pembrolizumab | The number of pembrolizumab treatment cycles was estimated by assuming that patients would receive pembrolizumab for a maximum number of cycles (35) unless they experienced disease progression (determined on the basis of the modelled PFS curve) earlier | High, likely to favour pembrolizumab |
| Continuation of treatment effect | The model assumed that the survival curves (both PFS and OS) for pembrolizumab would converge with that for BV at 8 years in the base case | High, likely to favour pembrolizumab |

BV = brentuximab; vedotin; OS = overall survival; PFS = progression-free survival

Source: Table compiled during the evaluation

6.33 The results of the economic evaluation are summarised below.

Table 9: Results of the economic evaluation

| | Pembrolizumab | Brentuximab vedotin | Increment |
|--|---------------|---------------------|---------------|
| As presented in the submission | | | |
| Costs | \$ [REDACTED] | \$257,572 | \$ [REDACTED] |
| Life years | 5.925 | 4.399 | 1.526 |
| Quality-adjusted life years | 4.568 | 3.330 | 1.238 |
| Incremental cost per life year gained | | | \$ [REDACTED] |
| Incremental cost per quality-adjusted life year gained | | | \$ [REDACTED] |
| Revised^a | | | |
| Costs | \$ [REDACTED] | \$267,288 | \$ [REDACTED] |
| Life years | 4.262 | 3.676 | 0.586 |
| Quality-adjusted life years | 3.284 | 2.782 | 0.502 |
| Incremental cost per life year gained | | | \$ [REDACTED] |
| Incremental cost per quality-adjusted life year gained | | | \$ [REDACTED] |

Notes: Numbers may not be exact due to rounding

^a It was noted that a monthly cycle length (rather than 3-week cycle) was incorrectly used in: 1) calculating the life years accrued each cycle for both treatment arms; 2) discounting the life years gained over time for the two treatment arms; and 3) calculating the accumulative costs and health outcomes over the model time horizon in the comparator BV arm. These errors were corrected during the evaluation.

Source: Table 3A.8-3, p137 of the submission. Revised results were recalculated during the evaluation.

6.34 As stated in the submission, one of the purposes of the economic evaluation was to determine an appropriate price advantage for pembrolizumab over BV on the assumption that the comparative treatment effect of pembrolizumab versus BV would be the same as assumed in the KN204 protocol. As such, the price of pembrolizumab proposed for the submission was calculated so that an incremental cost-effectiveness ratio (ICER) of \$45,000/QALY - \$75,000/QALY was the result of the hypothetical economic evaluation. It would remain for PBAC consideration whether \$45,000/QALY - \$75,000/QALY is an acceptable cost-effectiveness threshold to determine the price of pembrolizumab. After revising the errors contained in the economic model³, the ICER in the base case would increase to \$105,000/QALY - \$200,000/QALY at the pembrolizumab price proposed by the submission (i.e. \$ [REDACTED] per cycle (4 x 50 mg vials)). The PSCR (p.4) acknowledged the error in the economic model, and stated that correcting for this error would require a decrease of [REDACTED] % on [REDACTED] per pembrolizumab 50 mg vial (\$ [REDACTED] decreased to \$ [REDACTED]). The revised pembrolizumab price would need to be lower using the effective BV price in the model.

³ It was noted that a monthly cycle length (rather than 3-week cycle) was incorrectly used in: 1) calculating the life years accrued each cycle for both treatment arms; 2) discounting the life years gained over time for the two treatment arms; and 3) calculating the accumulative costs and health outcomes over the model time horizon in the comparator BV arm.

Table 10: Result of economic analysis, using the pembrolizumab price to achieve an ICER of \$ [REDACTED]/QALY (\$ [REDACTED] per 50mg vial, [REDACTED]% price reduction for pembrolizumab price, PSCR p.4)

| | Pembrolizumab | Brentuximab vedotin | Increment |
|--|---------------|---------------------|---------------|
| Costs | \$ [REDACTED] | \$267,288 | \$ [REDACTED] |
| Quality-adjusted life years | 3.284 | 2.782 | 0.502 |
| Incremental cost per quality-adjusted life year gained | | | \$ [REDACTED] |

6.35 The economic result was subject to the following additional assumptions:

- Patients in the pembrolizumab arm would not receive BV following pembrolizumab treatment failure. The ESC considered that this assumption was not representative of the likely use of these medicines in the PBS context. The PSCR (p.3) acknowledged that adjustment for treatment switching would be required should it occur to a great extent in the KN204 trial, and proposed that the economic model be updated to account for the costs of any treatments which are received post progression if observed in KN204.
- Patients would receive pembrolizumab or BV for the maximum number of cycles, unless they experience disease progression earlier. The PSCR (p.3-4) acknowledged that the maximum number of cycles for pembrolizumab and BV in the economic model did not reflect clinical practice, as treatment discontinuations due to reasons other than disease progression were not accounted for. However, the PSCR claimed that this was likely biased against pembrolizumab. The ESC was not convinced, noting the lack of comparative data on the treatment duration for pembrolizumab versus BV.
- The results of PFS and OS for BV reported in Study 0003 in subjects who failed ASCT prior to study enrolment would be applicable to patients who are ineligible for ASCT. The ESC considered this approach may not be conservative, because how patient characteristics and prognosis differ for patients who are ASCT naïve versus post ASCT and what consequences these may have on the comparative effectiveness of pembrolizumab versus BV are unknown.
- The ESC noted that the costs for progression-free and progressed-disease states were based on a Canadian study which may not be representative of the Australian clinical setting.

The ESC considered that the above assumptions did not reflect clinical practice or were not supported by clinical evidence. Their impacts on the ICER result, however, could not be examined given the lack of relevant study/trial data.

6.36 The results of the key sensitivity analyses presented are summarised below. The ESC considered that sensitivity analyses exploring different methods of extrapolation would also have been informative.

Table 11: Results of univariate sensitivity analyses

| Description of sensitivity analysis | | Incremental costs | Incremental QALYs | ICER |
|--|--|----------------------------|--------------------|----------------|
| Base case | | \$ [REDACTED] | 0.502 | \$ [REDACTED] |
| Costs | | | | |
| Drug costs only | | \$ [REDACTED] | 0.502 | \$ [REDACTED] |
| 50% of the listed BV costs | | \$ [REDACTED] | 0.502 | \$ [REDACTED] |
| 30% increase in PF costs | | | | \$ [REDACTED] |
| Hazard ratio (hypothetically set at 0.600 for OS and 0.622 for PFS in base case) | | | | |
| Reduction of treatment effect in terms of OS by 50% (OS HR of 0.800, no change in PFS HR) ^a | | \$ [REDACTED] | 0.334 | \$ [REDACTED] |
| Reduction of treatment effect in terms of PFS by 50% (PFS HR of 0.811, no change in OS HR) ^a | | \$ [REDACTED] | 0.448 | \$ [REDACTED] |
| Reduction of treatment effect in terms of both PFS and OS by 50% (0.800 and 0.811 for OS and PFS) | | \$ [REDACTED] | 0.280 | \$ [REDACTED] |
| No superior treatment effect in terms of OS (OS HR of 1.00, no change in PFS HR) ^a | | \$ [REDACTED] | 0.113 | \$ [REDACTED] |
| No superior treatment effect in terms of PFS (PFS HR of 1.00, no change in OS HR) ^a | | \$ [REDACTED] | 0.404 | \$ [REDACTED] |
| No superior treatment effect in terms of both OS and PFS (both HR of 1.00) ^a | | \$ [REDACTED] ^b | 0.000 ^b | Not calculable |
| Application of assumed HRs (2 years in base case, after which time point the survival curves start to converge) | | | | |
| 1 year | | \$ [REDACTED] | 0.569 | \$ [REDACTED] |
| Time horizon/Point of convergence of survival curve for both PFS and OS (both 8 years in base case) | | | | |
| Time horizon | Point of convergence of survival curve | | | |
| 5 years | 5 years | \$ [REDACTED] | 0.292 | \$ [REDACTED] |
| | 8 years | \$ [REDACTED] | 0.391 | \$ [REDACTED] |
| | 10 years | \$ [REDACTED] | 0.420 | \$ [REDACTED] |
| 8 years | 8 years | \$ [REDACTED] | 0.502 | \$ [REDACTED] |
| | 10 years | \$ [REDACTED] | 0.632 | \$ [REDACTED] |
| 10 years | 10 years | \$ [REDACTED] | 0.677 | \$ [REDACTED] |

BV = brentuximab vedotin; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OS = overall survival; PF= progression-free; PD = progressive disease; PFS = progression-free survival; QALY = quality-adjusted life year

Notes: Numbers may not be exact due to rounding

^a Sensitivity analyses conducted during the evaluation

^b Results after correcting the submission's error in calculating the survival estimates for pembrolizumab. The submission calculated the rates of disease progression and mortality per cycle in the pembrolizumab arm by multiplying hazard ratios to respective transition probabilities in the BV arms for the first 2 years. This methodological error was not corrected in the base case and in other sensitivity analyses given its negligible impacts on the ICER result (<3% change).

Source: Table compiled during the evaluation. The submission incorrectly used a cycle length of 1 month in calculating some costs and health outcomes (see the table note under Table 9). These errors were corrected in the base case analysis and the sensitivity analyses.

6.37 A key driver of the model was the cost of BV, including the price of BV and the number of cycles of BV. This is unsurprising given the high costs per patient per course of treatment. Reducing the BV price by 50%, the ICER would increase from \$105,000/QALY - \$200,000/QALY in the base case to more than \$200,000/QALY.

- 6.38 Arbitrary assumptions were made to explore the magnitude of the impact of the comparative treatment effect on the ICER result. Applying a less favourable HR for OS (0.80 vs 0.60 in the base case) increased the ICER by 36%. However, a less favourable HR for PFS (0.822 vs 0.611 in the base case) would result in an ICER favourable to pembrolizumab. This was because a reduced number of patients in the PFS health state for pembrolizumab would incur lower drug costs over the time horizon of the model. The ICER would increase approximately 3.5 fold (more than \$200,000/QALY vs \$105,000/QALY - \$200,000/QALY in the base case), if pembrolizumab was equivalent to BV for OS (HR of 1.00) but not for PFS (HR of 0.622 as in the base case). Assuming the survival curves (both OS and PFS) for pembrolizumab and BV would converge at an earlier time point (5 years vs 8 years in the base case), the ICER would increase considerably to more than \$200,000/QALY (61% change). The ESC considered that the effectiveness of pembrolizumab relative to BV was the major uncertainty for both the clinical and economic evaluations.
- 6.39 Other variables, eg utilities, time point of extrapolation, method of extrapolation and discounting rate, did not have major impacts on the estimate for the cost-effectiveness of pembrolizumab versus BV.

Cost-minimisation to BV

- 6.40 The Pre-PBAC response (p.1-2) stated that, as the submission's clinical claim was changed to that of non-inferiority against BV, the economic model proposed in the submission was no longer relevant. The PBAC considered that this was reasonable.
- 6.41 The Pre-PBAC response (p.1) suggested the cost-minimisation to BV be calculated on the basis that the average cost per patient for pembrolizumab is the same as that for BV. The PBAC noted the average number of vials per administration for BV is 3.14 and for pembrolizumab the number of vials would be four. BV has a weighted price across the ASCT eligible and ineligible populations, which should flow through to pembrolizumab, given the same requested PBS listings across both settings. The PBAC noted the median duration of follow-up in KN-087 was only 10.1 months and given treatment will continue until disease progression, the average duration of therapy in the study would be underestimated. Using the mean modelled duration of therapies of [REDACTED] cycles for BV and pembrolizumab, respectively, offered a potential solution to assessing same average cost for treatment for the next several years, until further directly comparative data is presented to PBAC for consideration and accepted. In the meantime, the PBAC considered that a longer duration of treatment for pembrolizumab than BV would be appropriate for the requested cost-minimisation approach because of the expected increased likelihood of use of immunotherapies beyond disease progression.

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

Drug cost/patient/cycle

- 6.42 The drug costs were estimated to be \$ [REDACTED] per patient per cycle for pembrolizumab and \$ [REDACTED] per patient per cycle for BV. These estimates were

based on: 1) the pembrolizumab price proposed in the PSCR and 4 x 50 mg vials of pembrolizumab per patient per cycle; 2) the PBS-listed price for BV and 3.14 x 50 mg vials of BV per patient per cycle; and 3) an assumption of [REDACTED]% of prescriptions being dispensed in public settings and [REDACTED]% in private settings. The drug costs per patient per course were estimated to be \$[REDACTED] for pembrolizumab and \$[REDACTED] for BV, based on the modelled treatment durations for pembrolizumab and BV used in the economic evaluation ([REDACTED] cycles for pembrolizumab and [REDACTED] cycles for BV). The economic model assumed that all patients would receive pembrolizumab or BV for the maximum number of cycles (35 cycles and 16 cycles, respectively) or until disease progression (using assumed HR for PFS of 0.622), whichever occurred earlier.

Estimated PBS usage & financial implications

- 6.43 This submission was not considered by DUSC. The submission took an epidemiological approach to estimate the number of patients that would be treated with pembrolizumab. The average number of administrations per patient for pembrolizumab was modelled using the assumed hazard ratio for progression free survival expected from Trial KN204. No existing evidence is available to support this estimate and therefore the actual number of administrations per patient expected in clinical practice, and the associated financial impact of listing pembrolizumab on the PBS, is uncertain.
- 6.44 In addition, the submission used expert opinion to estimate the number of patients in each of the arms in the treatment algorithm, without providing any details on the survey of the experts. The estimated number of eligible patients is uncertain.
- 6.45 The submission did not consider the use of BV after failure of pembrolizumab. If BV is used after failure of pembrolizumab in clinical practice, the estimated cost offset from replacing BV would be overestimated and therefore the financial impact of listing pembrolizumab would have been underestimated. The ESC considered that the cost offsets assumed in the submission were optimistic.
- 6.46 The financial estimates proposed in the Pre-PBAC response (p.2) assumed that both pembrolizumab ([REDACTED]%) and BV ([REDACTED]%) would share the third line market (replacement setting), ensuring cost neutrality to the Australian Government. Acknowledging the difficulty in estimating the financial impact of pembrolizumab and BV use in the fourth line setting, the Pre-PBAC response assumed that [REDACTED]% of third-line patients will require access to fourth line treatment with either pembrolizumab or BV, depending on their previous therapy (displacement setting), and estimated that the net cost to the Commonwealth for pembrolizumab use in fourth line therapy would be less than \$10 million per year in the first five years of listing.
- 6.47 Noting ESC's concerns regarding the optimistic cost-offsets attributed to the replacement of BV, the Pre-PBAC response (p.2) maintained that the listing of pembrolizumab on the basis of non-inferiority will remain cost neutral to the Commonwealth in the third line of therapy (replacement setting), but estimated that the net cost to the Commonwealth for pembrolizumab use in fourth line therapy

(displacement setting) would be less than \$10 million per year in the first five years of listing.

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

Quality Use of Medicines

- 6.48 The submission noted that the sponsor will provide updated information to physicians, nurses, pharmacists and patients, education programs and a '1-800' telephone medical information service to ensure appropriate use of pembrolizumab including identifying and managing potential immune-related adverse events.

Managed Entry Scheme/Managed Access Programme

- 6.49 In its submission, the sponsor proposed a Managed Entry Scheme/Managed Access Programme (MES/MAP), acknowledging the uncertainties surrounding its clinical claim of superiority given the limitations of the evidence (indirect comparison of non-transitive single-arm studies) upon which the claim was based. However, in its later pre-PBAC response, the sponsor noted the MES proposal was no longer relevant. The rationale for the initially proposed MES/MAP was that the sponsor believed that the clinical data provided in the submission were sufficient to warrant PBS listing as soon as possible, with uncertainty regarding the extent of the price advantage to be resolved upon the reporting of the ongoing head-to-head KN204 trial in 2019. KN204 is assessing the comparative effectiveness and safety of pembrolizumab versus BV in patients with rrcHL who have not had previous treatment with BV, and either 1) have failed to achieve a response or progressed after ASCT, or 2) are not ASCT candidates and have received at least 2 prior multi-agent chemotherapy regimens. The primary outcomes are PFS and OS. To resolve the uncertainties related to the evidence, interim data on PFS and OS would be presented in 2019. Final OS data, which depend on event rates stipulated in the trial protocol, are due in 2021. The submission also indicated that, upon availability of the KN204 data, model inputs such as (but not restricted to) observed and fitted OS and PFS Kaplan-Meier curves, treatment effect duration, AE rates and utilities would be updated.
- 6.50 The MES framework (now also referred to as the Managed Access Program (MAP) framework) is focused on submissions where the available data indicate a significant net benefit of the proposed medicine, but the magnitude of the benefit is uncertain until more conclusive evidence becomes available in a reasonable time frame that would resolve the uncertainty. PBAC has the discretion to recommend PBS listing at a higher price justified by the existing evidence with the option of requiring the sponsor to pay a future rebate (including interest) if the new data fail to deliver on the claimed benefits. The submission's economic evaluation, however, did not provide a basis for determining an initial price for pembrolizumab on the basis of the current available evidence, rather the initial price is based on a hypothetical treatment effect. The ESC did not consider a price advantage for pembrolizumab over BV was justified by the existing clinical evidence.

- 6.51 The ESC considered that the evidence provided in the submission was an inadequate basis for PBS listing under the MES/MAP framework, as:
- The superiority claim of pembrolizumab versus BV was not supported by the available clinical evidence (see Clinical claim);
 - The submission's economic evaluation did not provide a robust basis for determining an initial price for pembrolizumab;
 - The value of sequential treatment with pembrolizumab and BV will remain unanswered by the KN204 trial. Moreover, the rapidly evolving clinical algorithm of immunotherapies in haematological malignancies made it difficult to predict the clinical landscape of HL by 2020.
- 6.52 The Pre-PBAC response (p.2) stated that, as the submission's clinical claim was changed to that of non-inferiority against BV, the MES/MAP arrangement proposed in the submission was no longer relevant. The PBAC considered that this was reasonable.

Financial Management – Risk Sharing Arrangements

- 6.53 The Pre-PBAC response (p.3) stated that, should pembrolizumab be recommended for listing on the basis of non-inferiority to BV, the sponsor would be willing to negotiate a Deed of Agreement with the Department to ensure that financial uncertainties are appropriately mitigated.

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation on whether pembrolizumab should be listed on the PBS for the treatment of rrcHL pending a positive TGA Delegate's overview, and further discussion with the sponsor on determining the basis of cost-minimisation against brentuximab vedotin (BV). In deciding to defer, the PBAC agreed with the sponsor that pembrolizumab treatment showed promising overall response rates in a heavily pre-treated, refractory patient population, and that the clinical claim of non-inferiority compared with BV was supported by the evidence provided. On that basis, a price advantage over BV was not justified in the submission, and not requested in the pre-PBAC response.
- 7.2 The PBAC considered that, for patients with rrcHL, the appropriate clinical place in therapy for pembrolizumab would be as primary treatment post ASCT failure, or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.
- 7.3 The PBAC advised that the application had evolved since the time of lodgement, it would be necessary to merge the requested initial restrictions for pembrolizumab to remove the separation according to ASCT status, resulting in a single initial restriction and a single continuation restriction. Additional comments by the PBAC regarding the proposed restriction included deleting the reference to CD30+ as being

unnecessary for pembrolizumab and removing the criterion in relation to multi-agent chemotherapy.

- 7.4 The PBAC noted that Reed-Sternberg cells in rrcHL patients overexpress PD-L1 according to evidence from current literature (see paragraph 2.3), and was satisfied that there should be no requirement for PD-L1 testing in rrcHL, as almost all tumours are PD-L1 positive.
- 7.5 The PBAC considered BV to be an appropriate primary comparator. As confirmed during the sponsor hearing, the PBAC considered that pembrolizumab would likely displace rather than replace, BV. The PBAC also considered that there was currently no comparative evidence to dictate the order of this sequential treatment.
- 7.6 The PBAC noted that the clinical data presented were based on a comparison across single-arm studies with no common reference arm, with the key pembrolizumab study (KN087) having immature data. The populations included in these studies were not comparable, as none of the patients in the BV study were ASCT naïve, and the majority of patients in the pembrolizumab studies were BV experienced. Additionally, the evidence for BV presented in the current submission (ITT of Study 0003) differed from the BV data considered by the PBAC in November 2016. Overall, the PBAC considered that any incremental benefit of pembrolizumab over BV was not quantifiable based on the data provided.
- 7.7 As highlighted in the sponsor hearing, the evidence from the pembrolizumab studies presented in the submission was consistent with the recent evidence from CheckMate-205⁴, a Phase II trial for nivolumab, a pharmacological analogue of pembrolizumab, for the treatment of rrcHL post ASCT failure. The data from CheckMate-205 was based on longer median follow-up than KN087 and provided PBAC with more confidence in the preliminary clinical outcomes for pembrolizumab.
- 7.8 The PBAC agreed with the ESC regarding the inadequacy of the comparative evidence to support the submission's claim of superiority. PBAC also agreed the initial price advantage requested for pembrolizumab over BV in the proposed MES/MAP listing was unjustified based on the economic evaluation provided and the rapidly evolving clinical algorithm of immunotherapies in haematological malignancies made it difficult to predict the clinical landscape of cHL by 2020 when the KN204 data would become available.
- 7.9 Due to the concerns raised by ESC, the pre-PBAC response (p.1) amended the sponsor's clinical claim to one of non-inferiority against BV. The PBAC considered, in the absence of further comparative evidence, that a cost-minimisation against BV would be an appropriate way forward. However, establishing the basis for determining the cost-neutrality per patient of pembrolizumab against BV required

⁴Abstract, 14th international conference on malignant lymphoma in Lugano, Switzerland
http://www.ascopost.com/News/57782?utm_medium=Email&utm_source=ExactTarget&utm_campaign=&utm_term=6760327

further consideration given uncertainties with the duration of use of these therapies. A formal proposal from the sponsor and further negotiation with the Department would be required to establish these equi-effective dose calculations (see paragraph 6.41 for more detail).

- 7.10 The PBAC noted that the financial estimates proposed in the Pre-PBAC response (p.2), but considered the overall financial impact remained uncertain without establishing the cost-minimisation of pembrolizumab to BV and the extent of BV displacement.
- 7.11 The PBAC considered that a PBS listing of pembrolizumab would result in sequential therapy involving BV, but noted there was no economic evaluation presented for this sequential therapy. Thus in order to maintain cost-effectiveness of PBS-listed drugs when either BV or pembrolizumab are used in HL, the PBAC advised that pembrolizumab join the BV RSA, with an appropriate increase to the cap to recognise the submission's estimated additional utilisation of pembrolizumab beyond the cost-minimisation against BV, and with a preference for [REDACTED] of expenditure above the cap.
- 7.12 The PBAC noted ESC's concerns regarding the development of graft versus host disease in patients receiving PD-L1 inhibitors post ASCT, and the Pre-PBAC response (p.1) indicating that the Product Information of pembrolizumab will include a statement noting that close monitoring for early evidence of transplant-related complications is recommended. As such, the PBAC considered that the treatment decision for patients following ASCT could be left at the prescriber's discretion without instruction from the PBS restriction, unless advised otherwise by the TGA in the future.
- 7.13 The PBAC agreed with the issues raised by ESC regarding the economic model presented in the submission; however, the Committee considered that since the submission's clinical claim was subsequently changed to that of non-inferiority against BV, the economic model and MES/MAP arrangement proposed in the submission were no longer relevant.

Outcome:

Deferred

ADDENDUM

CHANGES TO PRESENT (OR RECOMMENDED) PBS AVAILABILITY

When the PBAC makes a recommendation under section 101(3) of the *National Health Act 1953* (“the Act”) in relation to a drug/medicinal preparation which it considers should be made available as a pharmaceutical benefit under Part VII of the Act, it is also required to consider whether the drug/medicinal preparation should be made available only in certain circumstances (see section 101(3C) of the Act). Where the PBAC considers that the drug/medicinal preparation should be made available only in certain circumstances, it specifies the circumstances in its recommendation under section 101(3).

At its meeting held on **18 August 2017**, the PBAC, in making its recommendation under section 101(3) of the Act, decided to recommend a change to the circumstances under which pembrolizumab is made available as a pharmaceutical benefit under Part VII of the Act.

A note of the PBAC’s decision follows.

PEMBROLIZUMAB, Powder for I.V. infusion, 50 mg and 100 mg vials, Keytruda[®], Merck, Sharp & Dohme (Australia) Pty Limited

8 Purpose of application

- 8.1 To inform the PBAC of a revised proposal from the sponsor on the basis of the cost-minimisation of pembrolizumab to brentuximab vedotin (BV), following a deferral based partially on this matter from the PBAC at its July 2017 meeting.

9 Background

- 9.1 At its July 2017 meeting, the PBAC deferred making a recommendation on whether pembrolizumab should be listed on the PBS for the treatment of relapsed or refractory classical Hodgkin’s Lymphoma (rrcHL) pending a positive TGA Delegate’s overview, and further discussion with the sponsor on determining the basis of cost-minimisation against BV. In deciding to defer, the PBAC had considered that pembrolizumab treatment showed promising overall response rates in a heavily pre-treated, refractory patient population, and that the clinical claim of non-inferiority compared with BV was supported by the evidence provided.
- 9.2 A revised proposal was received from the sponsor in response to the July 2017 PBAC minutes, addressing the issues raised in the minutes about the restriction, the basis

for cost-minimisation, utilisation estimates and the proposed Risk Sharing Arrangement (RSA). See Section 3 for details of the sponsor's proposal.

- 9.3 A positive TGA delegate's overview and the ratified resolution of the TGA's Advisory Committee on Medicines (ACM) meeting was available to the Committee prior to the August 2017 Special PBAC meeting.
- 9.4 The clinical evidence was unchanged from the July 2017 submission.

For more detail on PBAC's view, see section 11 "PBAC outcome".

10 Current proposal

Restriction

- 10.1 The sponsor agreed with the PBAC's advice to remove the separation according to autologous stem cell transplant (ASCT) status in the proposed PBS restrictions, resulting in a single initial and a single continuation restriction. The sponsor also agreed to the removal of the reference to CD30+ and multi-agent chemotherapy in the requested restriction.

Cost-minimisation

- 10.2 The sponsor accepted the PBAC's suggestion that the cost-minimisation analysis be based on estimated mean modelled durations of therapies of [REDACTED] cycles for BV and pembrolizumab, respectively, and on estimated mean number of vials per administration of 3.14 and 4 (of 50 mg each) for BV and pembrolizumab, respectively. Based on these estimates, the sponsor stated that the ex-manufacturer's price for pembrolizumab would therefore be \$ [REDACTED] per 50 mg vial.
- 10.3 The sponsor acknowledged that the above price estimate was based on the published price of BV, and that the final price of pembrolizumab would have to be determined using the effective price of BV, under the above dose and duration estimates.

Estimated PBS usage and financial implications

- 10.4 The sponsor's proposal assumed a [REDACTED]% share of the third-line market for pembrolizumab, and claimed that listing of pembrolizumab in the third-line setting would be cost neutral to the Commonwealth.
- 10.5 The sponsor also acknowledged that it was difficult to estimate the financial impact with the use of pembrolizumab and BV in the fourth-line setting. Therefore, in order to calculate the number of patients who were alive and progressed to the fourth-line setting to receive treatment with either pembrolizumab or BV depending on their

previous therapy, the difference between the extrapolated OS and PFS rates in each year for patients treated with pembrolizumab or BV was calculated separately and applied to the third-line treatment population in the sponsor’s proposal. In addition, a higher treatment uptake rate of █% was assumed for pembrolizumab in these estimates, claiming that this was consistent with the uptake rate observed for targeted therapies and immunotherapies in other cancer indications in the current clinical setting.

10.6 Based on the above assumptions, the sponsor claimed that the net cost to the PBS for the usage of pembrolizumab in the fourth-line setting would be less than \$10 million in the first year of listing, with a total of \$30 - \$60 million in the first six years of listing.

Table 12: Estimated PBS usage and financial implications in the fourth-line of treatment

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|--------|--------|--------|--------|----------|--------|
| Patients with rrcHL treated in 4L therapy | █ | █ | █ | █ | █ | █ |
| Pembrolizumab | \$█ | \$█ | \$█ | \$█ | \$█ | \$█ |
| Brentuximab vedotin | \$█ | \$█ | \$█ | \$█ | \$█ | \$█ |
| Estimated cost to the PBS and RPBS | \$█ | \$█ | \$█ | \$█ | \$█ █ | \$█ |

Source: sponsor’s proposal prior to the August 2017 PBAC Special meeting

Risk Sharing Arrangement

10.7 The sponsor proposed a █% rebate of costs above the agreed annual subsidisation caps for use beyond the agreed utilisation estimates, noting that:

- a █% rebate above expenditure caps was consistent with the other RSAs that are currently in place between the sponsor and the Commonwealth;
- given the unmet clinical need and small patient population as seen with the recent PBS listing of vorinostat for the treatment of cutaneous T-cell lymphoma (CTCL), the sponsor claimed that it was unlikely that the agreed subsidisation cap would be exceeded, and if it does, the financial impact would be minimal;
- the sponsor considered that this would compensate for the sponsor’s additional administration costs in having an RSA.

For more detail on PBAC’s view, see section 11 “PBAC outcome”.

11 PBAC outcome

- 10.8 The PBAC recommended the Authority Required listing of pembrolizumab for the treatment of rrcHL, on a cost-minimisation basis against BV.
- 10.9 In making this recommendation, the PBAC considered that pembrolizumab treatment showed promising overall response rates in a heavily pre-treated, refractory patient population, and that the clinical claim of non-inferiority compared with BV was supported by the clinical evidence provided.
- 10.10 The PBAC noted the sponsor's agreement to its previous advice on the proposed restriction criteria (paragraph 7.3, pembrolizumab minutes, July 2017 PBAC meeting). The PBAC also advised that the maximum number of repeats for the initial prescription should be increased from 5 to 6, while the maximum number of repeats for each continuing therapy prescription should be decreased from 7 to 6, so that the total corresponds to the maximum number of cycles (35) allowed overall.
- 10.11 The PBAC noted the sponsor's agreement to its previous advice on the appropriate basis of cost-minimisation against BV, based on estimated mean modelled durations of therapies of [REDACTED] cycles for BV and pembrolizumab, respectively, and on estimated mean number of vials per administration of 3.14 and 4 (of 50 mg each) for BV and pembrolizumab, respectively. Additionally, the PBAC advised the price of the 100 mg pembrolizumab vials should be estimated on the same principles.
- 10.12 The PBAC considered that the sponsor's estimates of a [REDACTED]:[REDACTED] market share, in favour of pembrolizumab, in the fourth line of therapy, was reasonable.
- 10.13 Noting its previous views on the uncertainty in the financial estimates due to displacement of BV, the PBAC maintained that a RSA would be required to mitigate the risks associated with the additional utilisation of pembrolizumab (paragraph 7.11). The PBAC considered that given the uncertainty around the potential for sequential use of BV and pembrolizumab, a sizeable rebate on costs above the agreed annual subsidisation caps should be put in place to manage the risk of use beyond the agreed utilisation estimates.
- 10.14 The PBAC advised that the Early Supply Rule should apply not to the listing of pembrolizumab.
- 10.15 The PBAC advised that under subsection 101(3BA) of the *National Health Act, 1953* that pembrolizumab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 10.16 The PBAC advised that pembrolizumab is not suitable for prescribing by nurse practitioners.

10.17 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:

Recommended

12 Recommended listing

10.18 Add new item:

| Name, Restriction, Manner of administration and form | Max. Amount | №.of Rpts | Dispensed price for maximum amount (DPMA) | Proprietary Name and Manufacturer |
|--|----------------|-----------|---|---|
| PEMBROLIZUMAB 50 mg vial for infusion, 1 100 mg vial for infusion, 1 | 200 mg | 6 | <i>To be confirmed</i> | Keytruda® Merck Sharp and Dohme Pty Ltd |

| | |
|------------------------------------|--|
| Category / Program | Section 100 – Efficient Funding of Chemotherapy |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Severity: | Relapsed or refractory |
| Condition: | Hodgkin lymphoma |
| PBS Indication: | Relapsed or refractory Hodgkin lymphoma |
| Treatment phase: | Initial treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined |

| | |
|---------------------------------------|---|
| <p>Clinical criteria:</p> | <p>Patient must have undergone an autologous stem cell transplant (ASCT) for this condition OR Patient must not be suitable for ASCT for this condition;</p> <p>AND</p> <p>Patient must have relapsed Hodgkin lymphoma following at least two prior treatments for this condition; OR</p> <p>Patient must have refractory Hodgkin lymphoma following at least two prior treatments for this condition;</p> <p>AND Patient must not have received prior treatment with a PD-1 inhibitor for this condition AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition</p> |
| <p>Prescriber Instructions</p> | <p>Applications for authorisation of initial treatment must be in writing and must include:</p> <p>(a) a completed authority prescription form;</p> <p>(b) a completed Hodgkin lymphoma pembrolizumab PBS Authority Application; and</p> <p>(c) a signed patient acknowledgement form.</p> |
| <p>Administrative Advice</p> | <p>No increase in the maximum number of repeats may be authorised.</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>Special Pricing arrangements apply.</p> <p>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).</p> <p>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</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p> |

Public Summary Document – July 2017 PBAC Meeting

| Name, Restriction, Manner of administration and form | Max. Amount | No. of Rpts | Dispensed price for maximum amount (DPMA) | Proprietary Name and Manufacturer |
|--|----------------|----------------|---|---|
| PEMBROLIZUMAB 50 mg vial for infusion, 1 100 mg vial for infusion, 1 | 200 mg | 6 | To be confirmed | Keytruda® Merck Sharp and Dohme Pty Ltd |

| | |
|------------------------------------|--|
| Category / Program: | Section 100 – Efficient Funding of Chemotherapy |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Severity: | Relapsed or refractory |
| Condition: | Hodgkin lymphoma |
| PBS Indication: | Relapsed or refractory Hodgkin lymphoma |
| Treatment phase: | Continuing treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined |
| Clinical criteria: | Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition. |
| Prescriber Instructions | 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). The treatment must not exceed a total of 35 cycles in a lifetime. |
| Administrative Advice | No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised Special Pricing Arrangements apply |

13 Context for Decision

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

14 Sponsor's Comment

MSD is pleased that the PBAC has recommended pembrolizumab for patients with relapsed or refractory classical Hodgkin's Lymphoma. MSD looks forward to working with the Department to enable patients to access pembrolizumab as soon as possible.