

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

1 Purpose

- 1.1 The early re-entry resubmission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for the treatment of early stage triple negative breast cancer in patients who have not received prior systemic therapy.
- 1.2 The resubmission was based on the PBAC decision to not recommend pembrolizumab for this indication at the March 2023 meeting. This resubmission addressed the issues raised by PBAC; see table below.

Table 1 Summary of key matters to be addressed

Matter of concern	Response	Addressed
Revision of inputs to the economic evaluation		
<u>Time horizon of 30 years</u> The PBAC considered that a 30-year time horizon was reasonable, in the context of more conservative treatment waning and given the aim of treatment is cure, in patients with eTNBC who are typically relatively young (para 7.8).	A time horizon of 30 years has been applied in the economic evaluation.	Yes
<u>Application of treatment waning from 5 years</u> The PBAC noted that the pre-PBAC response proposed applying treatment waning from 8 years, which resulted in a 9.35% OS benefit after 30 years. The PBAC considered that this remained optimistic, particularly in the context of immature OS data, and considered it would be appropriate to apply treatment waning from 5 years to reflect the clinical course of eTNBC (para 7.8).	The application of treatment waning has been applied at 5.5 years.	Not fully addressed
<u>Inclusion of adjustment of costs and outcomes to include adjuvant capecitabine</u> As adjuvant capecitabine was considered an appropriate comparator to pembrolizumab for patients with residual disease, the PBAC considered that it would be appropriate for the model to include adjustment to account for capecitabine use in these patients, as applied in the pre-PBAC revised base case (para 7.9).	Adjustment of costs and outcomes to include adjuvant capecitabine to the comparator arm have been applied in the economic evaluation.	Yes
<u>Revision of terminal care costs to \$6,050</u> The PBAC also considered that revision of the terminal care costs to \$6,050, in the pre-PBAC revised base case was appropriate and consistent with terminal care costs in the sacituzumab govitecan submission (para 7.9).	Terminal care costs of \$6,050 have been applied in the economic evaluation.	Yes

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Matter of concern	Response	Addressed
<p>ICER of less than \$35,000 per QALY The PBAC considered that an ICER of up to \$35,000/QALY gained would account for the uncertainty regarding the modelled outcomes (para 7.10).</p>	<p>The price of pembrolizumab has been reduced from \$ [redacted] to \$ [redacted] AEMP per 100 mg vial, resulting in an ICER of \$ [redacted]³/QALY.</p>	<p>Not fully addressed</p>
<p>Revision of inputs to the financial estimates</p>		
<p>Removal of the prevalent population from the patient numbers The PBAC considered that newly diagnosed eTNBC patients would begin treatment immediately or be enrolled on an access program, therefore inclusion of a prevalent pool of patients (other than Grandfather patients) overestimated the number of patients in year 1 (para 7.11).</p>	<p>The prevalent population was removed from the eligible pool. The number of patients eligible for grandfathering was also increased from [redacted]¹ to [redacted]².</p>	<p>Yes</p>
<p>Uptake in the adjuvant setting The PBAC considered the amendment of uptake in the adjuvant setting from 100% of patients treated in the neo-adjuvant setting to 75% was reasonable and was consistent with the KN-522 trial. However, the PBAC noted that if olaparib is listed for patients with BRCAm early breast cancer the utilisation of adjuvant pembrolizumab would be expected to decrease to around 60% of neo-adjuvant patients as olaparib would be the preferred adjuvant treatment for the 15% of patients with BRCAm (para 7.11).</p>	<p>The proportion of patients receiving adjuvant treatment set at 75% in the financial estimates. Olaparib was not recommended at the March 2023 PBAC meeting.</p>	<p>Yes</p>
<p>RSA across early and metastatic settings</p>		
<p>The PBAC considered that listing of pembrolizumab in eTNBC should result in offsets for pembrolizumab utilisation in the locally advanced metastatic TNBC setting from patients without disease progression and patients who progress but are not eligible for retreatment with pembrolizumab (para 7.11). The PBAC considered that an RSA across early and metastatic settings would be required, with appropriate offsets in mTNBC to account for cured patients and early relapsers</p> <ul style="list-style-type: none"> • Assuming 8% cured • At least 16% patients who have relapsed following eTNBC treatment with pembrolizumab (not eligible for retreatment with pembrolizumab) (para 7.12) 	<p>The submission noted this will be addressed post recommendation as part of the Deed negotiations.</p>	<p>Not fully addressed</p>

Source: 6.08 pembrolizumab Public Summary Document (PSD), March 2023 PBAC meeting

The redacted values correspond to the following ranges:

¹ <500

² 500 to <5,000

³ \$35,000 to < \$45,000

2 Background

2.1 Pembrolizumab was approved by the TGA on 2 September 2022 for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.

2.2 The PICO from the previous submission is presented below.

Table 2 Key components of the clinical issue addressed by the submission (as stated in the Mar 2023 submission)

Component	Description
Population	High risk early-stage triple negative breast cancer (TNBC) patients who have not had prior systemic therapy administered for newly diagnosed, locally advanced, centrally confirmed TNBC.
Intervention	Neoadjuvant: Pembrolizumab (200 mg IV) every 3 weeks in combination with paclitaxel + carboplatin for 4 cycles then pembrolizumab + doxorubicin/epirubicin + cyclophosphamide for 4 cycles, for a total of 8 cycles (24 weeks) followed by: Adjuvant: Pembrolizumab (200 mg IV) every 3 weeks as a single agent for up to 9 cycles (27 weeks)
Comparator	Standard chemotherapy guided by physician for the neoadjuvant phase, and placebo in the adjuvant phase
Outcomes	Pathological complete response (pCR), event-free survival (EFS), overall survival (OS), safety, quality of life (QoL)
Clinical claim	In patients with high-risk early-stage triple negative breast cancer, who have not had prior systemic therapy administered, pembrolizumab in combination with chemotherapy as neoadjuvant therapy, followed by pembrolizumab monotherapy post-surgery is superior to chemotherapy alone in terms of efficacy and inferior in terms of safety.

Source: Table 1.1-1, p4 of the March 2023 submission.

For more detail on PBAC’s view, see section 5 PBAC outcome.

3 Requested listing

3.1 The resubmission made amendments to the previously considered PBS restriction in response to the PBAC’s recommendations (para 7.2-7.3, pembrolizumab PSD, March 2023 PBAC meeting):

- It would be appropriate for the indication to specify Stage 2-3 eTNBC to limit use to the high-risk population and considered it was not necessary to include criteria specifying HER2 and HR status in the restriction as TNBC in the indication was sufficient to define the patient population.
- A single restriction combining neoadjuvant and adjuvant treatment would be preferable, with a limit on the total treatment duration aligned with the KN-522 trial and a requirement for patients to discontinue treatment where disease recurrence is evident.
- The restrictions should specify that treatment initiation is in combination with chemotherapy.
- It would be appropriate for the listing to remain silent regarding capecitabine use, to allow use in combination with adjuvant pembrolizumab where clinically appropriate, noting that there is some safety data for this combination from other settings.

3.2 The resubmission’s proposed restrictions did not address the PBAC’s recommendation that the restrictions should exclude combination use of pembrolizumab and olaparib (for patients with BRCAm) as this combination is unlikely to be cost-effective and there is a lack of safety and efficacy data to support it (para 7.3, pembrolizumab PSD, March 2023 PBAC meeting). As olaparib was not recommended for early breast cancer at the

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March 2023 PBAC meeting, the PBAC considered the restriction need not specifically exclude combination use with olaparib.

3.3 The resubmission also noted that the restriction has been revised to allow treatment initiated via non-PBS subsidised supply (i.e. ‘grandfathered’ patients, sponsor compassionate access programs).

3.4 The resubmission’s revised restrictions are outlined below.

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
PEMBROLIZUMAB Injection	NEW (Public) NEW (Private)	400 mg	7
Available brands			
Keytruda (pembrolizumab 100 mg/4 ml injection, 4 ml vial)			
Authority Required (STREAMLINED)			
Severity: Stage II or Stage III			
Condition: triple negative breast cancer			
Indication: Stage II or Stage III triple negative breast cancer			
Treatment Phase: [blank]			
Clinical criteria:			
The condition must have been (up until this drug therapy) untreated			
AND			
Clinical criteria:			
The condition must have been (up until this drug therapy) untreated with programmed cell death-1/ligand 1-1 (PD-1/PD-L1) inhibitor therapy in breast cancer			
AND			
Clinical criteria:			
Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of no higher than 1 prior to treatment initiation			
AND			
Clinical criteria:			
The treatment must be initiated in combination with chemotherapy			
AND			
Clinical criteria:			
Treatment criteria:			
Patient must be undergoing initial treatment with this drug – this is the first prescription for this drug; or			
Patient must be undergoing continuing treatment with this drug – both the following are true: (i) the condition has not progressed on active treatment with this drug, (ii) this prescription does not extend PBS subsidy beyond 12 cumulative months from the first administered dose			
AND			

Treatment criteria:
Patient must be undergoing treatment with this drug administered once every 3 weeks - prescribe up to 7 repeat prescriptions; or
Patient must be undergoing treatment with this drug administered once every 6 weeks - prescribe up to 4 repeat prescriptions.
Administrative Advice: No increase in the maximum amount or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised

- 3.5 The PBAC considered that the restriction could be silent on the patient’s WHO performance status as the majority of patients with early stage TNBC would be expected to have a WHO ECOG <2 at treatment initiation.
- 3.6 The PBAC reiterated that the restriction should ensure that treatment with pembrolizumab is initiated in combination with neoadjuvant chemotherapy. The PBAC considered that it would be reasonable to allow prevalent patients already initiated on neoadjuvant chemotherapy to begin treatment with pembrolizumab prior to surgery. However, PBAC considered it would not be appropriate for patients to initiate pembrolizumab after surgery (in the adjuvant setting) as effectiveness and cost-effectiveness have not been established for adjuvant treatment alone.
- 3.7 The PBAC considered that treatment with pembrolizumab under this restriction should be limited to a total of 52 weeks of treatment covering both adjuvant and neoadjuvant phases, assuming disease progression/recurrence had not occurred first.
- 3.8 With respect to the potential for re-treatment with PDL-1 inhibitor therapy in the event of metastatic disease, the PBAC considered that PBS-subsidy for re-treatment with pembrolizumab should not be available as there is no clinical evidence to support such use. The PBAC noted that the restrictions for mTNBC recommended at the March 2023 PBAC meeting include criteria preventing PBS-subsidised retreatment with pembrolizumab.

For more detail on PBAC’s view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item.

Consumer comments

- 4.2 The PBAC noted and welcomed the input from individuals (53), health care professionals (2) and organisations (4) via the Consumer Comments facility on the PBS website. The PBAC recalled the input received regarding the March 2023 submission, where comments from patients noted that pembrolizumab trials demonstrated a clear pCR and EFS benefit in the eTNBC setting. Consumers who had received

pembrolizumab noted the good quality of life they had on it and others noted the psychosocial benefits of giving hope and reducing fear by knowing there was an additional form of treatment that could reduce their risk of disease progression. Comments described the unmet treatment need for patients with early TNBC, noting the high cost to patients of self-funding pembrolizumab treatment.

- 4.3 The PBAC also recalled there was strong support from healthcare providers for the March 2023 submission, noting decreased mortality and morbidity rates for patients treated with pembrolizumab based on EFS and pCR outcomes in KN-522. The comments also noted that side effects are largely manageable and complicated immune-related side effects that substantially impact patients are uncommon. However, there is risk of long term immune mediated toxicities including permanent endocrinopathies, which is more relevant in the early breast cancer setting where treatment is with curative intent. Comments also noted that pembrolizumab is standard of care for eTNBC in other countries and there is a high clinical need for patients with TNBC.
- 4.4 The PBAC noted that comments received from individuals and healthcare professionals in relation to the resubmission reflected the same issues and concerns as those received in relation to the March 2023 submission.
- 4.5 The PBAC recalled that comments from consumer groups Pink Hope and Breast Cancer Network Australia (BCNA) provided their support for the March 2023 pembrolizumab submission. Comments described TNBC patients as typically young, meaning they often have young families and work responsibilities that are impacted substantially by their diagnosis. The comments also described the need for new, effective targeted treatments for TNBC and the importance of subsidised access to treatment, given its high cost. The comments noted that a pCR allows patients to hope and plan for the future and is a significant outcome. Patients reported a willingness to risk AEs if there is potential to prevent recurrence of disease and are well-placed to consider potential side-effects with their treatment team. Regarding the July 2023 resubmission the BCNA noted that the PBAC recommendation for pembrolizumab in the metastatic TNBC setting was welcome, but patients shouldn't have to wait for their early disease to recur to access treatment in the metastatic stage, where outcomes are worse, and delays to funding have substantial negative impacts on patients.
- 4.6 Comments from Peter MacCallum Cancer Centre and Medical Oncology Group of Australia (MOGA) supported the March 2023 pembrolizumab submission, noting that clinical trials have shown that pembrolizumab reduced the risk of relapse, with improved EFS at 3 years, while being well-tolerated in addition to chemotherapy. Regarding the July 2023 submission MOGA emphasized the value of pCR in improving prognosis and the likelihood that the demonstrated gains in pCR and PFS would result in improved overall survival. MOGA also stated that patient selection is important to manage immune related adverse events and multidisciplinary communication is required to ensure women are fit to proceed safely to surgery, and in particular,

monitoring for endocrinopathies, which may occur late.

- 4.7 MOGA expressed its strong support for the current pembrolizumab submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the KN-522 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab which was a Grade A. This is the highest grade on a scale from A to C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies.¹

Clinical evaluation

- 4.8 No additional clinical evidence was provided.

Economic analysis

Time horizon and treatment waning

- 4.9 The base case economic model in the previous submission extrapolated outcomes to 30 years and generated a greater increment in EFS (and consequently OS) over time. By the end of the 30-year time horizon, the model estimated an increment of 24.5% EFS events compared with 7.7% at the longest follow-up from KN-522 (36 months). The PBAC considered it was not clinically plausible for the EFS increment to continue to increase beyond 5 years as the vast majority of TNBC relapse occurs within the first 5 years. The PBAC considered it would be appropriate to apply treatment waning from 5 years to reflect the clinical course of eTNBC. The PBAC noted that the use of a 30-year time horizon, where the trial median follow-up was just over 3 years and OS data were immature, introduced additional uncertainty into the modelled outcomes. However, the PBAC considered that a 30-year time horizon was reasonable, in the context of more conservative treatment waning and given the aim of treatment is cure, in patients with eTNBC who are typically relatively young.
- 4.10 The resubmission used a time horizon of 30 years with waning applied at 5.5 years, rather than 5 years as requested by the PBAC. The resubmission argued that this was reasonable and conservative as pembrolizumab is likely to extend the time to relapse compared with standard care. The modelled difference in overall survival at the end of the 30-year time horizon when applying treatment waning at 5.5 years is 6.7% which, the resubmission argued, is very likely under-estimated in the context of the incremental pCR rate being 7.5%.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

- 4.11 Applying treatment waning from 5.5 years instead of 5 years increased the incremental QALYs gained over the 30 year time horizon from 0.75 to 0.81 QALYs. With waning applied at 5.5 years, at the end of the 30 year time horizon the model estimated an increment of 6.9% EFS events. If waning is applied at 5 years, the model estimates an increment of 6.3% EFS events after 30 years.

Capecitabine adjustment

- 4.12 Adjustment of costs and outcomes to include adjuvant capecitabine to the comparator arm have been applied in the economic evaluation as PBAC considered appropriate.

Terminal care costs

- 4.13 The PBAC also considered that revision of the terminal care costs to \$6,050, in the pre-PBAC revised base case was appropriate and consistent with terminal care costs in the sacituzumab govitecan submission. The terminal care cost in the resubmission has been amended to \$6,050.

Revised pembrolizumab cost and ICER

- 4.14 The PBAC considered that an ICER of up to \$35,000/QALY gained would account for the uncertainty regarding the modelled outcomes (para 7.10, pembrolizumab PSD, March 2023 PBAC meeting). The resubmission proposed a revised price for pembrolizumab of \$| AEMP per 100 mg vial. This was reduced from \$| in the previous submission and \$| in the pre-PBAC response to the previous submission. The above changes and the revised price for pembrolizumab result in an ICER of \$35,000 to < \$45,000/QALY gained.
- 4.15 The price per vial required for an ICER of \$35,000/QALY would be \$█. The price required for an ICER of \$35,000/QALY with waning applied from 5 years would be \$|.
- 4.16 The resubmission noted that the requested price is below the price considered cost-effective in mTNBC (\$| per 100mg vial, which was recommended with an ICER of \$75,000 to < \$95,000/QALY).
- 4.17 The resubmission noted that the ICER would be reduced further if a lower discount rate was applied.
- 4.18 The resubmission stated that it is likely that the modelled survival curves from KN-522 that adjust for capecitabine use only in the comparator arm are conservative, as PBAC considered that there may be some use of pembrolizumab in combination with capecitabine, and the proposed restrictions do not prevent such use. However, no efficacy data for combination use of pembrolizumab and capecitabine were available and there are uncertainties regarding the adjustment applied for capecitabine use in the comparator arm, therefore this approach may not be conservative.
- 4.19 The resubmission considered that the ICER of \$35,000 to < \$45,000/QALY may be an overestimate given the conservative assumptions applied and argued that the true

ICER could reasonably be as low as \$25,000 to < \$35,000/QALY (applying treatment waning from 5.5 years and 3.5% discount rate).

Drug cost/patient/course

- 4.20 At the revised price of pembrolizumab, the resubmission's economic model estimated a total undiscounted cost for pembrolizumab of \$| per patient, per course (\$| in the neoadjuvant setting and \$| in the adjuvant setting). Based on the number of scripts per patient in the financial estimates (15.07) the total cost per patient is \$|
- 4.21 The number of cycles in the financial estimates (15.07) was based on extrapolation of the KN-522 study as per the Pre-Sub-Committee Response for the March 2023 submission, however in the resubmission adjusted model the number of cycles was 13.0 (7.48 neoadjuvant and 5.53 adjuvant). The pre-PBAC response noted that the time on treatment in the economic model accounted for the fact that only ~75% of patients who received neoadjuvant treatment went on to receive adjuvant treatment with pembrolizumab. The financial estimates separately assumed 75% of initiating patients did not receive adjuvant treatment with pembrolizumab. Therefore applying a duration of 5.53 cycles to the 75% of patients treated with pembrolizumab in the financial estimates would underestimate the treatment duration in the adjuvant setting. The PBAC noted that after accounting for this adjustment the treatment duration in the financial estimates still appeared to be overestimated compared to the modelled time on treatment (approximately 7.37 cycles for patients treated in the adjuvant setting). The PBAC considered that the financial estimates should be revised to reflect the number of cycles in the economic model.
- 4.22 The treatment duration assumed in the financial estimates for grandfathered patients was 7.53 cycles (total).

Estimated PBS usage & financial implications

- 4.23 The resubmission revised the financial estimates to remove the prevalent population from the eligible pool and set the proportion of patients receiving adjuvant treatment to 75%, in line with the PBAC's advice. The resubmission also applied the new effective price (AEMP of \$| per 100 mg vial). In addition to these changes the resubmission increased the number of patients eligible for grandfathering from < 500 to 500 to < 5,000, noting the current enrolment in patient programs is approximately 20 patients per week. Grandfather patients were assumed to have half the treatment duration as treatment would have already been initiated.
- 4.24 These changes reduced the number of patients and scripts in year 1, with no changes to patient numbers and scripts in years 2 to 6. The co-payment amounts in the revised worksheets were also updated to \$30 (General) and \$7.30 (Concessional/Safety Net), though this was not noted in the resubmission. The financial estimates are shown in Table 3.

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- 4.25 The annual cost to PBS/RPBS was estimated to be \$50 million to < \$60 million in year 1, decreasing to \$40 million to < \$50 million in years 2 to 6. The total cost to the PBS/RPBS in the first 6 years of listing was estimated to be \$200 million to < \$300 million. Applying a reduced duration of treatment (7.48 neoadjuvant cycles and 7.37 adjuvant cycles per paragraph 4.21) reduced the total annual cost to the PBS/RPBS to \$50 million to < \$60 million in year 1, decreasing to \$40 million to < \$50 million in years 2 to 6. The revised total cost to the PBS/RPBS in the first 6 years of listing was estimated to be \$200 million to < \$300 million.
- 4.26 Listing of pembrolizumab for eTNBC would have an impact on its use in mTNBC for patients with CPS ≥ 10 (recommended at the March 2023 PBAC meeting). The resubmission’s financial estimates did not include cost offsets from reduced pembrolizumab utilisation in the mTNBC setting, therefore the net impact is overestimated.

Table 3 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 (incl. ¹ Grandfathered)	1	1	1	1	1	1
Number of scripts dispensed	2	2	2	2	2	2
Estimated financial implications of pembrolizumab						
Net cost to PBS/RPBS	4	3	3	3	3	3
Net cost to MBS	5	5	5	5	5	5
Net cost to PBS/RPBS/MBS	4	3	3	3	3	3
Net cost to PBS/RPBS (treatment duration revised to 14.85 cycles)	4	3	3	3	3	3

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 10,000 to < 20,000

³ \$40 million to < \$50 million

⁴ \$50 million to < \$60 million

⁵ \$0 to < \$10 million

Financial Management – Risk Sharing Arrangements

- 4.27 The sponsor stated it is willing to enter into an RSA with the Commonwealth on sharing the costs of the subsidy for supply of pembrolizumab for the treatment of early, high risk TNBC, in order to manage any risk to the overall cost to the PBS. The PBAC noted that if recommended, a combined deed with mTNBC would need to reduce patient numbers for mTNBC to account for 8% cured and at least 16% recurrent after pembrolizumab, and therefore ineligible for pembrolizumab in metastatic TNBC (para 7.12 pembrolizumab PSD, March 2023 PBAC meeting). The resubmission stated that adjustment of the patient numbers will be addressed post recommendation as part of the Deed negotiations. The Pre-PBAC stated that determination of the net financial impact across eTNBC and mTNBC collectively was not possible at the time of

PBAC consideration as finalisation of the financial agreed estimates for mTNBC was ongoing.

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended the listing of pembrolizumab for the treatment of early stage triple negative breast cancer. The PBAC noted there is a high clinical need for effective treatment in this patient population, who are typically young and have a poor prognosis. The PBAC considered that the amendments made in the resubmission, including changes to the economic evaluation and a reduced price, had sufficiently addressed the Committee's previous concerns.
- 5.2 The PBAC considered that following its recommendation for listing of pembrolizumab for mTNBC at its March 2023 meeting, there remained a high clinical need for effective treatment in the early TNBC setting. This was also reflected in the consumer comments received in relation to the resubmission.
- 5.3 The PBAC noted that the revised restriction had appropriately addressed its previous advice (see paragraph 3.1). In addition, the PBAC considered that the restriction need not specify the patient's WHO performance score for patients with early stage disease and that treatment should be initiated in combination with neoadjuvant chemotherapy, consistent with use in the KN-522 trial. The PBAC recalled that the restrictions for pembrolizumab for treatment of mTNBC recommended at the March 2023 PBAC meeting included criteria preventing PBS-subsidised retreatment with pembrolizumab and considered that this remained appropriate.
- 5.4 The PBAC recalled it had previously accepted the claim of superior comparative effectiveness was reasonable, with pembrolizumab in combination with chemotherapy providing a meaningful improvement in event free survival, compared with standard chemotherapy alone, however overall survival data were immature. The PBAC noted that the resubmission did not present any additional clinical data. The PBAC requested that OS data from KN-522 be provided to the PBAC when it is available.
- 5.5 The PBAC noted that the resubmission appropriately addressed the PBAC's concerns regarding the economic model in terms of the time horizon, revision of terminal care costs, and adjustment of the costs and outcomes to include adjuvant capecitabine. The PBAC noted that the resubmission's revised model applied waning from 5.5 years, rather than 5 years as requested by the PBAC. The PBAC recalled it considered it was not clinically plausible for the EFS increment to continue to increase beyond 5 years as the vast majority of TNBC relapse occurs within the first 5 years. The resubmission argued that applying waning from 5.5 years was reasonable and conservative as pembrolizumab is likely to extend the time to relapse compared with standard care. The PBAC considered that application of waning from 5.5 years was acceptable, based

on the modelled differences in OS and PFS at the end of the 30-year time horizon, which appeared plausible.

- 5.6 The PBAC previously considered that with the specified revisions to the economic model (as per paragraph 7.12 pembrolizumab PSD, March 2023 PBAC meeting) pembrolizumab would be acceptably cost-effective at a price that gives an ICER of less than \$35,000 per QALY. The resubmission proposed a revised price for pembrolizumab of \$1,100 per 100 mg vial, resulting in an ICER of \$35,000 to < \$45,000/QALY gained with revisions to the economic model as per paragraph 5.5. The PBAC noted that the requested price was below the price considered cost effective in the mTNBC setting (\$1,100), in keeping with the broader patient population in the earlier setting and the necessary extensive extrapolation of the clinical data in the economic model. The PBAC considered that at the price proposed, the ICER was within an acceptably cost-effective range for the early TNBC setting.
- 5.7 The PBAC noted the resubmission revised the financial estimates to apply the revised effective price, remove the prevalent population from the eligible pool, and set the proportion of patients receiving adjuvant treatment to 75%, in line with the PBAC's advice. The PBAC considered that these changes were appropriate. In addition to these changes the resubmission increased the number of patients eligible for grandfathering from <500 to 500 to < 5,000. The PBAC considered the financial estimates should be revised to reflect the same number of pembrolizumab treatment cycles as in the economic model. The PBAC also considered that the net financial impact should be revised to account for offsets due to reduced use of pembrolizumab in the metastatic setting, assuming an additional 8% of patients are cured in the early setting with pembrolizumab (based on the difference in EFS at 36 months in KN-522) and at least 16% who have relapsed following eTNBC treatment and would not be eligible for retreatment with pembrolizumab (based on progression events in the pembrolizumab arm of KN-522 at 36 months).
- 5.8 The PBAC noted the sponsor proposed a risk sharing arrangement including use in both early stage disease and metastatic disease. The PBAC considered a risk sharing arrangement with a 100% rebate on utilisation above agreed caps would be appropriate to address uncertainty in estimating the overall cost to the PBS across both early stage disease and metastatic disease and the potential for use outside the proposed restrictions (e.g. retreatment in metastatic or advanced disease) where cost-effectiveness has not been established.
- 5.9 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for pembrolizumab:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over chemotherapy alone in terms of pCR, EFS and potentially

OS;

- b) The treatment is expected to address a high and urgent unmet clinical need as there are currently no immunotherapies listed on the PBS for treatment of eTNBC; and
- c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

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

Outcome:

Recommended

6 Recommended listing

6.1 Add new indication as follows:

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
PEMBROLIZUMAB Injection	NEW (Public) NEW (Private)	400 mg	7
Available brands			
Keytruda (pembrolizumab 100 mg/4 ml injection, 4 ml vial)			
Restriction Summary [new 1] / Authority Required (STREAMLINED)			
	Severity: Stage II or Stage III		
	Condition: triple negative breast cancer		
	Indication: Stage II or Stage III triple negative breast cancer		
	Clinical criteria:		
	The treatment must be initiated in combination with neoadjuvant chemotherapy		
	AND		
	Clinical criteria:		
	The condition must not have progressed/recurred whilst on treatment with this drug		
	AND		
	Treatment criteria:		
	Patient must not be undergoing treatment with this drug beyond 52 cumulative weeks under this restriction.		
	AND		
	Treatment criteria:		
	Patient must be undergoing treatment with this drug administered once every 3 weeks - prescribe up to 7 repeat prescriptions; or		

	Patient must be undergoing treatment with this drug administered once every 6 weeks - prescribe up to 4 repeat prescriptions.
	Administrative Advice: No increase in the maximum amount or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

7 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.

8 Sponsor's Comment

MSD welcomes the positive recommendation made by the PBAC and is working closely with the Department of Health and Aged Care to ensure that pembrolizumab is available to Australian early-stage triple negative breast cancer patients as soon as possible.