

An addendum to this Public Summary Document has been included at the end of the document.

## 6.07 PEMBROLIZUMAB,

**Solution concentrate for I.V. infusion 100 mg in 4 mL,  
Keytruda<sup>®</sup>,  
Merck Sharp & Dohme (Australia) Pty Ltd.**

### 1 Purpose of submission

- 1.1 The Category 1 submission requested a Section 100 (Efficient Funding of Chemotherapy Program) Authority Required listing for pembrolizumab for the treatment of patients with advanced endometrial cancer who have disease progression following prior systemic therapy.
- 1.2 The submission originally requested listing of pembrolizumab, in combination with lenvatinib, in all patients regardless of biomarker status, and listing of pembrolizumab monotherapy for those patients with deficient DNA mismatch repair (dMMR) endometrial cancer. The Advisory Committee on Medicines (ACM) Advice became available during evaluation, and subsequently the sponsor updated the requested listing for pembrolizumab to be for use:
- in combination with lenvatinib for patients with mismatch repair proficient (pMMR) endometrial cancer; and
  - as monotherapy for patients with deficient DNA mismatch repair (dMMR) endometrial cancer.
- 1.3 The requested basis for listing was a cost utility analysis of pembrolizumab plus lenvatinib compared to chemotherapy (doxorubicin or paclitaxel). Table 1 presents the key components of the clinical issue addressed by the submission and Pre-Sub-Committee Response (PSCR).

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

Component	Description
Population	Patients with advanced, recurrent or metastatic endometrial cancer that have progressed following prior treatment.
Intervention	Pembrolizumab 200 mg IV every 3 weeks for up to 35 cycles as monotherapy (in dMMR) or in combination with lenvatinib 20 mg oral daily (in pMMR).
Comparator	Doxorubicin 60mg/m <sup>2</sup> IV Q3W or Paclitaxel 80mg/m <sup>2</sup> IV QW (3 weeks on/1 week off). In the dMMR subgroup, a near term comparator is dostarlimab 500mg Q3W for 4 doses, then 1000mg Q6W.
Outcomes	Overall survival, progression-free survival, objective response rate, health-related quality of life, safety
Clinical claim	Pembrolizumab plus lenvatinib in pMMR: superior in terms of efficacy with an inferior safety profile compared with chemotherapy. Pembrolizumab monotherapy in dMMR: superior efficacy and safety versus chemotherapy.

Source: Table 1.1-1, p4 of the submission, Table 1, p5 of the PSCR.

dMMR = deficient mismatched repair; IV = intravenous; mg = milligram; pMMR = mismatch repair proficient; Q3W = every three weeks; Q6W every six weeks

## 2 Background

### Registration status

#### Combination therapy

- 2.1 Pembrolizumab received TGA approval on 7 February 2022 for the following indication:
- “pembrolizumab in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation”.
- 2.2 As outlined above, this differs from the proposed TGA indication at the time the submission was lodged, which did not restrict use of combination therapy with pembrolizumab and lenvatinib based on mismatch repair status. The sponsor originally requested listing of pembrolizumab, in combination with lenvatinib, in all patients regardless of biomarker status, and listing of pembrolizumab monotherapy for those patients with deficient DNA mismatch repair (dMMR) endometrial cancer.
- 2.3 Due to the change to the registered indication, the Pre-Sub-Committee Response (PSCR) amended the proposed treatment algorithm and restriction to:
- pembrolizumab plus lenvatinib in patients with pMMR EC (rather than all-comers, which had been proposed in the submission),
  - pembrolizumab monotherapy in patients with dMMR EC.
- 2.4 The sponsor provided the following information in relation of the impact of this change to the proposed PBS population: “Given the ITT results of KN775 (combination treatment) were applied in the economic model, and acted as a proxy for KN158 (monotherapy in dMMR), and that the submission requested a PBAC recommendation on the basis of net cost per patient, the change in the TGA indication is not anticipated to impact the estimate of cost effectiveness. Likewise, it does not affect the Section 4 budget impact analysis (also based on net cost per patient). However, the changed TGA indication will mean a change to the restriction wording, which we will clarify in the PSCR once we have confirmation from the TGA.”
- 2.5 As background to the rationale for restricting use of pembrolizumab plus lenvatinib combination therapy to patients with pMMR EC, the TGA Delegate had requested ACM advice regarding the following questions:
- What is the view of the ACM regarding the contribution of each of lenvatinib and pembrolizumab in the proposed indication?
  - What is the view of the ACM regarding the proposed indication that does not define the patient population based on mismatch repair status of the tumour? Is limitation of the indication to mismatch repair proficient tumours warranted? (pembrolizumab and lenvatinib ACM Minutes, December 2021).



this indication appears to be subsequent data from KN158 (with longer follow-up and increasing sample size). The pre-PBAC response stated that the sponsor “|||||||”.

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

### 3 Requested listing

3.1 The restrictions proposed in the PSCR are outlined below.

#### Elements of listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Lenvatinib 4 mg/10 mg, 30 Capsules	2	60 capsules	2	\$6,471.22 published price	LENVIMA, Eisai Australia Pty Ltd
Name, restriction, manner of administration, form	Maximum amount (units)		No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Pembrolizumab 100 mg injection, 1 vial	200 mg		6	\$7,881.87 (private) published price	KEYTRUDA, Merck Sharp & Dohme (Australia) Pty Ltd
	200 mg		6	\$7,733.78 (public) published price	

#### Pembrolizumab (in combination with lenvatinib) for pMMR

<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction Type – assessment time by Services Australia – Method of obtaining authority approval (if Authority Required)</b> <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)
<b>Severity:</b> advanced, metastatic or recurrent
<b>Condition:</b> proficient mismatch repair endometrial carcinoma
<b>Indication:</b> Advanced, metastatic or recurrent proficient mismatch repair (pMMR) endometrial carcinoma
<b>Treatment Phase:</b> Initial treatment
<b>Clinical criteria:</b> The condition must have progressed on prior platinum-based chemotherapy regimen in the first-line advanced, metastatic or recurrent setting, i.e. not including any platinum-based chemotherapy administered in the neo-adjuvant or adjuvant setting AND Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor, or prior tyrosine kinase inhibitor for endometrial cancer AND Patient must have a WHO performance status of 0 or 1 AND Patient must have proficient mismatch repair (pMMR) endometrial cancer, as determined by immunohistochemistry test AND

*Public Summary Document – March 2022 PBAC Meeting with March 2023 Addendum*

<p>The treatment must be in combination with PBS subsidised lenvatinib for this indication, unless an intolerance to lenvatinib requires a temporary or permanent dose reduction or discontinuation of lenvatinib</p> <p>AND</p> <p>The treatment must not exceed a total of 7 doses under this restriction</p>
<p><b>Administrative Advice:</b> In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later</p>
<p><b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.</p>
<p><b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised</p>
<p><b>Treatment Phase:</b> Continuing treatment</p>
<p><b>Clinical criteria:</b></p> <p>Patient must have previously received PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition.</p> <p>AND</p> <p>The treatment must be in combination with PBS subsidised lenvatinib for this indication, unless an intolerance to lenvatinib requires a temporary or permanent dose reduction or discontinuation of lenvatinib</p> <p>AND</p> <p>The treatment must not exceed a total of 35 cycles or up to 24 months of treatment in a lifetime for this condition</p>
<p><b>Administrative Advice:</b> In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later</p>
<p><b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.</p>
<p><b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised</p>
<p><b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 888 333</p>
<p><b>Treatment Phase:</b> Grandfathered</p>
<p><b>Clinical criteria:</b></p> <p>Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date]</p> <p>AND</p> <p>The condition must have progressed on prior platinum-based chemotherapy regimen in the first-line advanced, metastatic or recurrent setting, i.e. not including any platinum-based chemotherapy administered in the neo-adjuvant or adjuvant setting</p> <p>AND</p> <p>Patient must have proficient mismatch repair (pMMR) endometrial cancer, as determined by immunohistochemistry test</p> <p>AND</p> <p>Patient must not have received prior PBS funded treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor or any prior tyrosine kinase inhibitor for endometrial cancer</p> <p>AND</p> <p>Patient must have stable or responding disease</p> <p>AND</p> <p>Patient must have a WHO performance status of 0 or 1</p> <p>AND</p> <p>The treatment must be in combination with PBS-subsidised treatment with lenvatinib for this indication, unless an intolerance to lenvatinib requires a temporary or permanent dose reduction or discontinuation of lenvatinib</p> <p>AND</p> <p>The treatment must not exceed a total of 35 cycles or up to 24 months of treatment in a lifetime for this condition</p>

*Public Summary Document – March 2022 PBAC Meeting with March 2023 Addendum*

<b>Administrative Advice:</b> In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised

**Lenvatinib (in combination with pembrolizumab) for pMMR**

<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction Type – assessment time by Services Australia – Method of obtaining authority approval (if Authority Required)</b> <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)
<b>Severity:</b> advanced, metastatic or recurrent
<b>Condition:</b> endometrial carcinoma
<b>Indication:</b> Advanced, metastatic or recurrent endometrial carcinoma
<b>Treatment Phase:</b> Initial treatment
Clinical criteria: The condition must have progressed on prior platinum-based chemotherapy regimen in the first-line advanced, metastatic or recurrent setting, i.e. not including any platinum-based chemotherapy administered in the neo-adjuvant or adjuvant setting AND Patient must not have received prior treatment with lenvatinib for endometrial cancer and the patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for endometrial cancer AND Clinical criteria: (combination treatment) Patient must have proficient mismatch repair (pMMR) endometrial cancer, as determined by immunohistochemistry test Patient must have a WHO performance status of 0 or 1 AND The treatment must be in combination with PBS-subsidised treatment with pembrolizumab for this condition
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b> 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. AND The treatment must be in combination with PBS-subsidised treatment with pembrolizumab for this condition
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333

Public Summary Document – March 2022 PBAC Meeting with March 2023 Addendum

<b>Treatment Phase:</b> Grandfathered
<p><b>Clinical criteria:</b>                  Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date]                  AND                  The condition must have progressed on prior platinum-based chemotherapy regimen in the first-line advanced, metastatic or recurrent setting, i.e. not including any platinum-based chemotherapy administered in the neo-adjuvant or adjuvant setting                  AND                  Patient must have proficient mismatch repair (pMMR) endometrial cancer, as determined by immunohistochemistry test                  AND                  Patient must not have received prior PBS funded treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor or any prior tyrosine kinase inhibitor for endometrial cancer                  AND                  Patient must have stable or responding disease                  AND                  Patient must have a WHO performance status of 0 or 1                  AND                  The treatment must be in combination with PBS-subsidised treatment with pembrolizumab for this condition</p>
<p><b>Administrative Advice:</b> In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later</p>
<p><b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.</p>
<p><b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised</p>

**Pembrolizumab monotherapy for dMMR**

<b>Pembrolizumab monotherapy</b>	
<b>Severity:</b>	Advanced, metastatic or recurrent
<b>Condition:</b>	Deficient mismatch repair (dMMR) endometrial carcinoma
<b>PBS Indication:</b>	Advanced, metastatic or recurrent deficient mismatch repair (dMMR) endometrial carcinoma
<b>Treatment phase:</b>	Initial
<b>Restriction:</b>	<input checked="" type="checkbox"/> Authority Required – Telephone <input checked="" type="checkbox"/> Authority Required – Electronic
<b>Clinical criteria:</b>	<p>The condition must have progressed on prior platinum-based chemotherapy regimen in the first-line advanced, metastatic or recurrent setting, i.e. not including any platinum-based chemotherapy administered in the neo-adjuvant or adjuvant setting                  AND                  Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for endometrial cancer                  AND                  Patient must have a WHO performance status of 0 or 1                  AND                  Patient must have deficient mismatch repair (dMMR) endometrial cancer, as determined by immunohistochemistry test                  AND                  The treatment must not exceed a total of 7 doses under this restriction</p>
<b>Treatment phase:</b>	Continuing
<b>Clinical criteria:</b>	<p>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                  AND                  The treatment must not exceed a total of 35 cycles or up to 24 months of treatment in a lifetime for this condition</p>

*Public Summary Document – March 2022 PBAC Meeting with March 2023 Addendum*

<b>Treatment Phase:</b>	Grandfathered
<b>Clinical Criteria:</b>	<p>Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date]</p> <p>AND</p> <p>The condition must have progressed on prior platinum-based chemotherapy regimen in the first-line advanced, metastatic or recurrent setting, i.e. not including any platinum-based chemotherapy administered in the neo-adjuvant or adjuvant setting</p> <p>AND</p> <p>Patient must not have received prior PBS funded treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for endometrial cancer</p> <p>AND</p> <p>Patient must have stable or responding disease</p> <p>AND</p> <p>Patient must have a WHO performance status of 0 or 1</p> <p>AND</p> <p>Patient must have deficient mismatch repair (dMMR) endometrial cancer, as determined by immunohistochemistry test</p> <p>AND</p> <p>The treatment must not exceed a total of 35 cycles or up to 24 months of treatment in a lifetime for this condition</p>

- 3.2 The submission noted that lenvatinib and pembrolizumab are each marketed by different companies. The Competition and Consumer Act 2010 prohibits concerted practices, anti-competitive agreements and cartel conduct. In the agreed final outcomes of a pre-submission meeting, the Department acknowledged that “Provision of list prices and requesting the PBAC make a recommendation on the basis of a net cost per patient is an acceptable way of navigating the challenges of intercompany working”.
- 3.3 Based on this, the submission only used the publicly available list prices in the economic analysis and financial estimates sections. A combined drug acquisition cost per patient was calculated and used in the economic and financial sections as a proxy for an effective price. No specific price per pack of lenvatinib or per vial of pembrolizumab were proposed in the submission.
- 3.4 The proposed restriction included the criterion: ‘Patient must have received a prior platinum-based chemotherapy regimen in the advanced, metastatic or recurrent setting, i.e. not including any platinum-based chemotherapy administered in the neo-adjuvant or adjuvant setting’. The PBAC advised that this should be amended to: ‘Patient must have received a prior platinum-based chemotherapy regimen for this condition’ so as to:
- allow use in patients who received platinum-based chemotherapy in later lines, consistent with the KN775 trial in which 9.7% of patients had received prior palliative hormonal therapy;
  - allow use in patients who progress after platinum-based chemotherapy (rather than requiring the patient to have ‘progressed on’ platinum-based chemotherapy); and
  - remove the distinction between the platinum-based chemotherapy having been

administered in the (neo)adjuvant versus the advanced setting, given there can be overlap between these settings.

- 3.5 The proposed restrictions limit treatment to patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, which aligned with KN775. The ESC and PBAC considered this criterion was reasonable for pembrolizumab plus lenvatinib combination therapy given the potential for toxicity.
- 3.6 The proposed restrictions allow use of either pembrolizumab or lenvatinib as single agents if a patient develops an intolerance. The PBAC considered that use of pembrolizumab as a single agent should also be permitted in patients in whom lenvatinib is contraindicated.
- 3.7 The submission proposed an ‘Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)’ listing, however the PBAC considered that an ‘Authority Required (streamlined)’ listing would be more appropriate.

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

## **4 Population and disease**

- 4.1 Endometrial cancer is the most common gynaecological cancer in Australia and the fifth most diagnosed cancer in Australian women (2016).<sup>1</sup> The incidence has risen 18% over the last 5 years (AIHW 2021). Most patients are postmenopausal and diagnosed after the age of 55, but the submission states that endometrial cancer is increasingly being diagnosed in younger women. Endometrioid carcinoma is the most common histologic type of endometrial cancer, and typically presents at an early stage with abnormal uterine bleeding, with a favourable prognosis. However, approximately 13% of all endometrial cancers recur (Fung Kee Fung 2006) and 18% of patients are diagnosed in the advanced or metastatic settings<sup>2</sup>. These cases are associated with a poor prognosis with a five-year relative survival of under 16% (AIHW 2021).
- 4.2 Endometrial cancers can be divided into pMMR or dMMR tumours. Currently, MMR status does not affect the decision to administer chemotherapy in the second line setting. In its consideration of ‘Testing for mismatch repair deficiency (dMMR) in endometrial cancer to help determine eligibility for PBS-subsidised dostarlimab’, the MSAC PASC noted that the prognostic value of the dMMR biomarker in EC was currently limited. (1674 Ratified PICO, p5)
- 4.3 The submission considered that dMMR testing was routine in practice, and had both diagnostic and prognostic utility.

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<sup>1</sup> <https://www.cancer.org.au/cancer-information/types-of-cancer/uterine-cancer>

<sup>2</sup> <https://seer.cancer.gov/statfacts/html/corp.html>

- 4.4 The TGA Delegate’s overview noted that “pMMR tumours have different gene expression and typically, but not invariably, a different immune phenotype to dMMR tumours. Fewer neoantigens are likely to be presented in pMMR tumours, including the expression of PD-L1. Preservation of MMR typically impacts the response of the tumour to checkpoint inhibitors and other treatment strategies, so combination therapies are an approach of interest.” (p7 of Delegate’s Overview).
- 4.5 The place in therapy proposed by the submission was for use after failure of first line platinum based chemotherapy. Based on the TGA indication, the PSCR proposed that the combination would be used in patients with pMMR tumours, while pembrolizumab monotherapy would be used in those with dMMR tumours.
- 4.6 The PBAC noted that a range of Phase III randomised, controlled trials are underway investigating the use of immunotherapies in the first-line setting.

## **5 Comparator**

- 5.1 The submission nominated doxorubicin or paclitaxel as the main comparators. The main arguments provided in support of this nomination were that though there is no standard of care for patients with advanced, recurrent or metastatic endometrial cancer who have progressed on prior systemic platinum-based chemotherapy, these are the most commonly used agents in the second line both overseas and in Australia. This was likely reasonable though no evidence was provided to support the claim regarding the prevalence of usage in Australia.
- 5.2 The submission noted that in rare cases, a patient who has had a long interval between the completion of systemic treatment and progression may be prescribed a rechallenge with carboplatin plus paclitaxel. The submission considered this does not occur frequently, as most patients progress rapidly. It should be acknowledged that hormonal therapies may also be used in the second line setting particularly in patients with positive estrogen receptors, though the response is modest.<sup>3</sup>
- 5.3 The submission also nominated dostarlimab, a PD-1 inhibitor, as a potential near market comparator in the dMMR subgroup of the target population.

*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. The clinician discussed the current lack of options for patients who have progressed after first-line therapy, with immunotherapies being the first major advance in endometrial cancer treatment for decades. The clinician discussed the benefits of pembrolizumab monotherapy in

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<sup>3</sup> van Weelden WJ, Massuger LFAG, ENITEC, Pijnenborg JMA and Romano A (2019) Anti-estrogen Treatment in Endometrial Cancer: A Systematic Review. *Front. Oncol.* 9:359. doi: 10.3389/fonc.2019.00359

dMMR patients including the long median duration of response observed in the single-arm KN158 study. The presenter also outlined the results of the KN775 combination therapy trial and discussed that clinicians are able to manage lenvatinib toxicity.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from health care professionals (3) and organisations (2) via the Consumer Comments facility on the PBS website. The comments outlined the high unmet need for effective therapies to treat this condition, and the statistically significant and clinically meaningful gain in OS observed in the KN775 trial. One health care professional outlined that it is standard practice for clinicians to make decisions based on the benefits versus risks of treatment, further stating that they considered it to be important for patients with dMMR endometrial cancer to have the option of either combination or monotherapy.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for this submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the KN775 and KN158 studies. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab plus lenvatinib combination therapy, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement) based on a comparison with chemotherapy; and, for pembrolizumab monotherapy, was limited to 3 based on a single-arm study.<sup>4</sup> ·

### **Clinical trials and studies**

- 6.4 The submission was based on one randomised controlled trial comparing pembrolizumab plus lenvatinib to placebo (Keynote-775, referred to as KN775; N = 827) and single arm studies of pembrolizumab plus lenvatinib (KN146; N=124), pembrolizumab monotherapy (KN158; N=90) and lenvatinib monotherapy (E-204; N=133).
- 6.5 Details of the trials and studies presented in the submission are provided in the table below.

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<sup>4</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Public Summary Document – March 2022 PBAC Meeting with March 2023 Addendum

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
<b>Pembrolizumab Plus lenvatinib</b>		
Keynote 775 (Study 309)	A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Cancer. Clinical Study Report V.Makker. et al. A multicenter, open label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer: Study 309/KEYNOTE 775 Colombo N, et al. Outcomes by Histology and Prior Therapy with Lenvatinib plus Pembrolizumab vs Treatment of Physician's Choice in Patients with Advanced Endometrial Cancer (Study 309/ KEYNOTE-775).	February 2021.  Virtual Annual Meeting on Women's Cancer. SGO 2021 [Abstract]  ESMO 2021 [Abstract]
Keynote 146 (E7080; A001-111)	A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors. Clinical study report. Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, Romeo M, Bratos R, Brose MS, DiSimone C, Messing M, Stepan DE, Dutcus CE, Wu J, Schmidt EV, Orlowski R, Sachdev P, Shumaker R, Casado Herraes A. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer.  Makker V, Rasco DW, Vogelzang NJ, et al. Lenvatinib + pembrolizumab in patients with advanced endometrial carcinoma: Updated results.  Makker V, Rasco D, Dutcus C, et al. A phase 1b/2 trial of lenvatinib (LEN) plus pembrolizumab (Pembro) in patients (Pts) with endometrial carcinoma.  Makker V, Rasco D, Vogelzang NJ, Brose MS, Cohn AL, Mier J, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial.	Date not provided.  J Clin Oncol. 2020;38(26):2981-2992  J Clin Oncol, 2018 (suppl; abstr 5596). Presented at: 54 <sup>th</sup> Annual Meeting of the American Society of Clinical Oncology (ASCO); 2018 Jun 1–5; Chicago, IL. ASCO poster no. 420. Presented at: 53 <sup>rd</sup> Annual Meeting of the American Society of Clinical Oncology (ASCO); 2017 Jun 2-6; Chicago, IL. ASCO abstract no. 5598, poster no. 420  Lancet Oncol. 2019;20(5):711-8.
	Taylor M, Dutcus CE, Schmidt E, et al. A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients with selected solid tumors.	Ann Oncol. 2016;27 (suppl 6):266-295. Presented at: European Society of Medical Oncology (ESMO) 2016 Congress; 2016 Oct 7-11; Copenhagen, Denmark. Abstract 776PD.
<b>Lenvatinib</b>		
E 7080-G000-204 (E204)	Vergote I., Powell M.A., Teneriello M.G., Miller D.S., Garcia A.A., Mikheeva O.N., Bidzinski M., Cebotaru C.L., Dutcus C.E., Ren M., Kadowaki T., Funahashi Y., Penson R.T. Second-line lenvatinib in patients with recurrent endometrial cancer.	Gynecologic Oncology 2020 156:3 (575-582).
<b>Pembrolizumab</b>		

Public Summary Document – March 2022 PBAC Meeting with March 2023 Addendum

Trial ID	Protocol title/ Publication title	Publication citation
<b>Pembrolizumab Plus lenvatinib</b>		
Keynote 158	O'Malley et al. Pembrolizumab in Patients with Microsatellite Instability-High (MSI-H) Advanced Endometrial Cancer: Updated Results From KEYNOTE 158.	ESMO 2021 virtual meeting presentation
<b>Dostarlimab (Near market comparator)</b>		
GARNET	Oaknin A., Tinker A, Gilbert L, Samouëlian V, Mathews C, Brown J, Barretina-Ginesta MP, Moreno V; Gravina A, Abdeddaim C, Banerjee S, Guo W, Danaee H, Im E, Sabatier R. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial.	JAMA Oncology 2020; 6(11):1766-1772.

Source: Table 2.2-1, p34-37 of the submission.

6.6 The key features of the included randomised trial and studies are summarised in the table below.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Combination pembrolizumab plus lenvatinib						
KN775	827	R, MC, OL Median F/U 11.4 mths	Low	All comers (84% pMMR: 16% dMMR)	OS, PFS, ORR HRQoL	Yes
KN146 (cohort 3-2L)	124 (108 in primary analysis)	SAS, median F/U 18.7 mths "Basket" study <sup>a</sup>	High	All comers (87% pMMR: 10% dMMR)	ORR at Week 24; ORR, DOR, PFS, OS,	Not used
Pembrolizumab monotherapy						
KN158 (cohort D+K)	90 EC patient	SAS, Median F/U 16.5 months; "Basket" study <sup>b</sup>	High	dMMR patients	ORR by cohort, ORR by biomarker, DoR, PFS, OS	Not used
Lenvatinib monotherapy						
E-204	133	SAS, OL, Median F/U 9.6 months	High	All comers <sup>a</sup>	ORR by cohort, PFS, OS,	Not used
Dostarlimab (near market comparator)						
GARNET	79	SAS, OL, F/U not presented	High	dMMR	OS, PFS, ORR	Not used

Source: p29 of the submission.

DB=double blind; dMMR = deficient mismatch repair; DoR= duration of response; EC = endometrial carcinoma; F/U = follow-up MC=multi-centre; MSI-H = microsatellite instability high; OL=open label; ORR = objective response rate; OS=overall survival; PFS=progression-free survival; pMMR = proficient mismatch repair; R=randomised. SAS = single arm study

<sup>a</sup> A total of 290 patients (286 treated) with different cancers enrolled in KN146 of which 125 had EC

<sup>b</sup> A total of 1,595 patients with different cancers enrolled in KN158 of which 90 had MSI-H/dMMR EC

<sup>c</sup> assumption, MMR status not measured as part of E-204

6.7 The comparative efficacy of the pembrolizumab plus lenvatinib combination in all-comers (i.e. in pMMR and dMMR patients) was supported by the KN775 trial. However, KN775 did not have a pembrolizumab monotherapy arm. Instead, to support the efficacy of pembrolizumab monotherapy, the submission relied on the results of the single arm KN158 and a side by side comparison with KN775 in the dMMR subpopulation.

- 6.8 The remaining studies (i.e. other than KN775) were non randomised, single arm studies, and would be expected to have a high risk of selection bias, and the lack of a control arm prevented any pre-specified statistical comparison.
- 6.9 The submission stated that in KN775, the total family-wise error rate (Type I error) among the primary PFS and OS outcomes, ORR analysis, and for both the pMMR and all-comer patients was controlled at one-sided 0.025 level. Analyses in the dMMR subgroup of KN775 were not included in the alpha spending as part of the planned statistical analysis; thus, while KN775 was stratified for MMR status, the results for the dMMR subgroup should be considered exploratory.
- 6.10 Patients randomised to pembrolizumab plus lenvatinib in KN775 were treated with pembrolizumab for up to 35 cycles (two years). However, patients who stopped treatment with stable disease or better were eligible for up to an additional year of treatment with pembrolizumab (17 cycles) ± lenvatinib if they progressed after stopping study treatment. The discontinuation rules for pembrolizumab in KN775 were not consistent with the proposed restriction, as patients would not be eligible for additional pembrolizumab if they have progressive disease. This may affect the applicability of efficacy estimates from KN775 and also the time on treatment (ToT) estimates used in the economic evaluation. It was noted that 9% of patients in the pembrolizumab plus lenvatinib arm of KN775 remained on treatment after 24 months based on the ToT data provided in the economic evaluation in the submission. The PSCR (p4) noted that the maximum ToT for pembrolizumab in the economic model was set at 24 months to reflect the proposed PBS listing.

### ***Comparative effectiveness***

- 6.11 A summary of the OS and PFS results from the included trials and studies is presented in Table 4.

Table 4: Summary of OS and PFS for combination treatment and monotherapy

Trial/ study	All comers			Subgroups						
	Median (months [95% CI])		HR (95% CI)	pMMR		dMMR		Median (months [95% CI])		HR (95% CI)
	Tx	Chemo		Tx	Chemo		Tx	Chemo		
KN-775	N	411	416		346	351	–	65	65	–
	OS	18.3 (15.2, 20.5) <sup>b</sup>	11.4 (10.5, 12.9)	<b>0.62<sup>c</sup></b> <b>(0.51, 0.75)</b>	17.4 (14.2, 19.9) <sup>b</sup>	12.0 (10.8, 13.3)	<b>0.68<sup>c</sup></b> <b>(0.56, 0.84)</b>	NR (NR, NR) <sup>b</sup>	8.6 (5.5, 12.9)	0.37 <sup>d</sup> (0.22, 0.62)
	PFS	7.2 (5.7, 7.6)	3.8 (3.6, 4.2)	<b>0.56<sup>c</sup></b> <b>(0.47, 0.66)</b>	6.6 (5.6, 7.4)	3.8 (3.6, 5.0)	<b>0.60<sup>c</sup></b> <b>(0.50, 0.72)</b>	10.7 (5.6, NR)	3.7 (3.1, 4.4)	0.36 <sup>d</sup> (0.23, 0.57)
KN-146	N	108		94			11			
	OS	16.7 (15.0, NR)		16.4 (13.5, 25.9)			NR (7.4, NR)			
	PFS	7.5 (5.0, 8.3)		5.4 (4.4, 7.6)			18.9 (3.9, NE)			
KN-158 <sup>a</sup>	N						79			
	OS						NR (27.2, NR)			
	PFS						13.1 (4.3, 34.4)			
E-204	N	133								
	OS	10.6 (8.9, 14.9)								
	PFS	5.6 (3.7, 6.3)								

Source: Table 2.5-2, p74 of the submission. CI = confidence interval; dMMR = deficient mismatch repair; HR = hazard ratio; OS = overall survival; PFS = progression free survival; pMMR = proficient mismatch repair.

<sup>a</sup> (PEM) (Cohort D+K)

<sup>b</sup> From product-limit (Kaplan-Meier) method for censored data.

<sup>c</sup> p<0.0001

<sup>d</sup> nominally p<0.0001 as per submission, but not part of formal statistical analysis plan and should be considered exploratory  
Note that the alpha value for PFS in KN775 was 0.0005 due to multiplicity adjustments, therefore a 95% confidence interval may not be informative

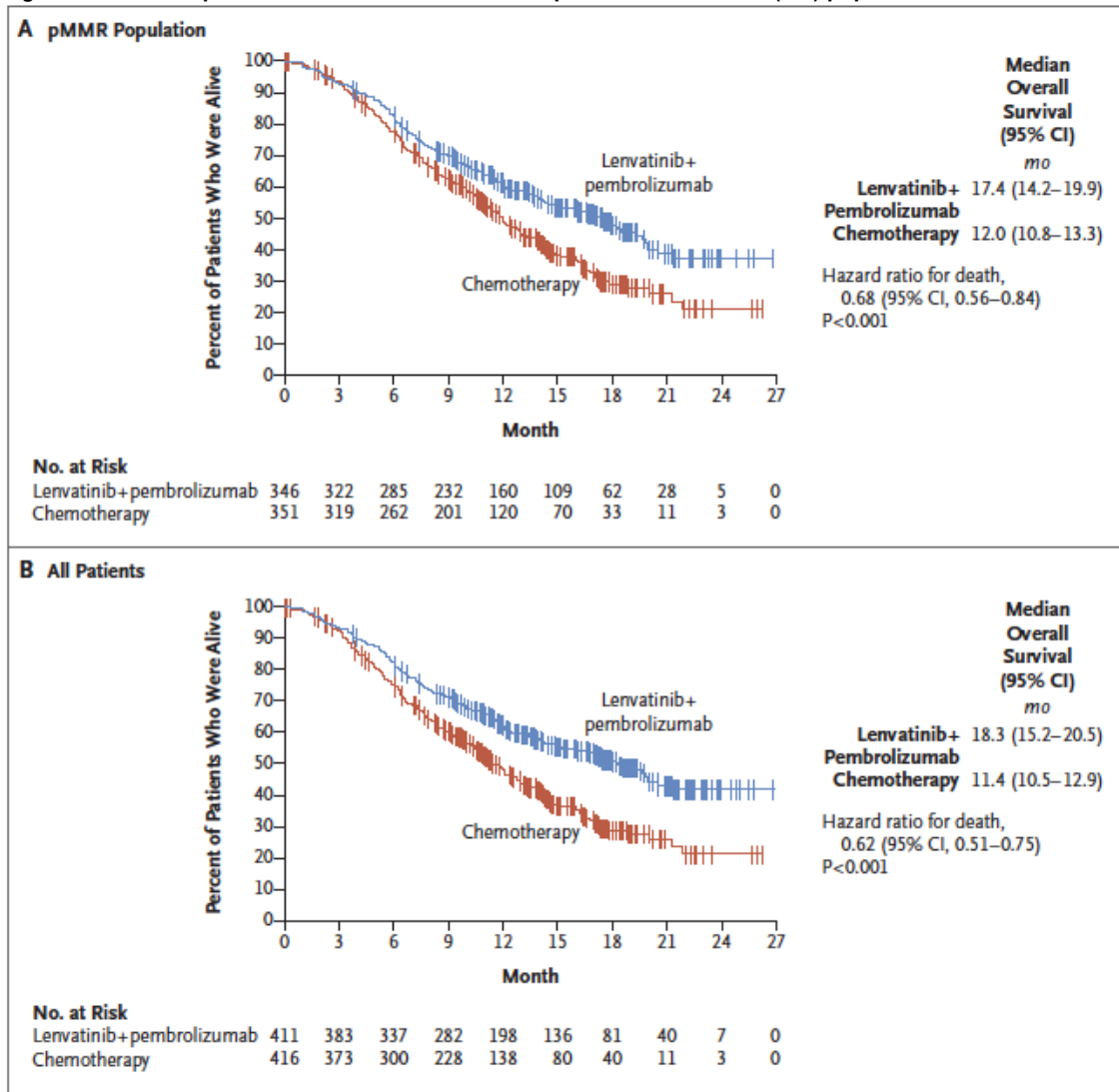
Text in bold indicate statistically significant results

### **Overall Survival: combination therapy**

- 6.12 At the first interim analysis (IA1) of KN775, after a median follow up of 11.4 months, patients in the pembrolizumab plus lenvatinib arm had a median survival that was significantly longer than those participants randomised to the chemotherapy arm (median OS 18.3 months (95% CI 15.2, 20.5) versus 11.4 months (95% CI 10.5, 12.9), HR = 0.62 (95% CI 0.51, 0.75)) in the all-comers population. The submission considered that this represented a clinically meaningful improvement in median survival of 6.9 months. The point estimate for the overall survival (OS) hazard ratio (HR) in KN775 for the all-comers population met the proposed MCID of OS HR = 0.75, which was based on the statistical power calculation in KN775.
- 6.13 The PBAC noted that the HR for OS was 0.68 (95% CI: 0.56, 0.84) in the pMMR subgroup, which was similar to the HR in the ITT population of 0.62 (95% CI: 0.51, 0.75). The PBAC further noted the HR in the dMMR subgroup was 0.37 (95% CI: 0.22, 0.62), but acknowledged this was an exploratory analysis.

6.14 Figure 1 illustrates the Kaplan-Meier estimates of OS in the pMMR and all-comers populations in KN775. Separation of the curves occurred about 3.5 months after initiation of the study. Although heavily censored, the submission noted that the curves continue to separate. The submission considered this demonstrated the significant improvement in survival for patients in the pembrolizumab plus lenvatinib arm compared to those in the chemotherapy arm of KN775.

Figure 1: KN775 Kaplan-Meier estimates of OS in the pMMR and all-comer (ITT) populations



Source: Makker, V et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N Engl J Med 2022; 386:437-448  
CI = confidence interval; mo = months

6.15 The ESC noted that, at the data-cut provided, the median follow-up was 11.4 months and 46% (188/411) of patients had died in the pembrolizumab plus lenvatinib arm. The ESC considered that, given the relatively short duration of follow-up, the OS data were immature but indicated a potential survival benefit.

6.16 The submission considered that the phase II single arm study in pembrolizumab plus lenvatinib participants (KN146) supported this survival estimate, with a median OS of

16.7 months (95% CI 15.0, not reached) at median follow up of 18.7 months. The submission acknowledged that the median survival in KN146 was lower than in KN775, which was likely due to the fact that the cohort of patients in KN146 were more heavily pre-treated; as 27.7% of patients in the pembrolizumab plus lenvatinib arm of KN775 had received 2 prior lines of treatment, whilst in KN146, 37.0% of patients had received 2 prior lines of systemic therapy, and an additional 10.2% had received 3 prior lines of systemic therapy.

- 6.17 In contrast, for the lenvatinib monotherapy phase II single arm study (E-204), patients treated with lenvatinib monotherapy reported a median OS of 10.6 months (95% CI 8.9, 14.9), which was similar to the median OS seen in the chemotherapy arm of KN775 of 11.4 months (95% CI 10.5, 12.9).

**Overall Survival: pembrolizumab monotherapy (dMMR)**

- 6.18 Cohorts D and K in the KN158 study did not include an all-comers population (dMMR only). Consequently, no data for pembrolizumab monotherapy in the pMMR population is available.
- 6.19 The submission noted that in the dMMR subgroups of KN775, KN146 and KN158, median OS was yet to be reached for either the pembrolizumab plus lenvatinib combination (KN775 and KN146) or for pembrolizumab monotherapy (KN158).
- 6.20 The submission also noted that, in the chemotherapy arm of KN775, median OS in the dMMR subgroup was 3.4 months shorter than that in the pMMR subgroup, indicating that for patients with the dMMR subtype chemotherapy is less effective. The submission also stated that this reduced efficacy with chemotherapy in an advanced dMMR tumour was similar to that seen in dMMR colorectal cancer, which was seen in the KN177 dMMR mCRC study, which was provided as the evidence for the PBAC recommendation for this indication in March 2021.
- 6.21 The evaluation considered there was no strong evidence to support the assertion that chemotherapy is less effective in patients with dMMR tumours compared to pMMR tumours given: the small sample size of the dMMR subgroup; and the wide confidence interval for OS in patients treated with chemotherapy which overlap for pMMR (median OS = 12.0 months, 95%CI 10.8, 13.3) and dMMR (median OS = 8.6 months, 95%CI 5.5, 12.9). The observed point difference in median OS in the chemotherapy arm between dMMR and pMMR may be due to chance. As noted in paragraph 4.2, the MSAC PASC noted that the prognostic value of the dMMR biomarker in EC was currently limited (1674 Ratified PICO, p5).
- 6.22 A naïve indirect comparison of the OS at landmark time points between KN775 and KN158 in the dMMR population is presented in Table 5.

**Table 5: Comparison of OS at landmark timepoints between KN775 and KN158 in dMMR patients**

OS time point	KN775		KN158 (Cohorts D + K)
	Pembrolizumab + Lenvatinib (N=65) % (95% CI)	Chemotherapy (N=65) % (95% CI)	Pembrolizumab (N=79) % <sup>a</sup>
<b>6 months</b>	80.0 (68.1, 87.9)	61.7 (48.5, 72.5)	82.3
<b>12 months</b>	67.2 (54.2, 77.2)	39.1 (26.7, 51.3)	69.4
<b>18 months</b>	63.5 (50.3, 74.1)	25.8 (14.2, 39.0)	67.9
<b>24 months</b>	63.5 (50.3, 74.1)	25.8 (14.2, 39.0)	64.0
<b>36 months</b>	NR	NR	60.1

Source: Table 2.5-6, p82 of the submission. CI = confidence interval; NR = not reported; OS = overall survival  
<sup>a</sup> 95% CI not presented for OS rates.

6.23 The proportion of patients remaining alive at the same time points were similar for the dMMR patients randomised to pembrolizumab plus lenvatinib in KN775 and patients treated with pembrolizumab monotherapy in KN158, and appear to be higher than patients treated with chemotherapy in KN775. However, the evaluation, ESC and PBAC considered that the results should be interpreted with caution as:

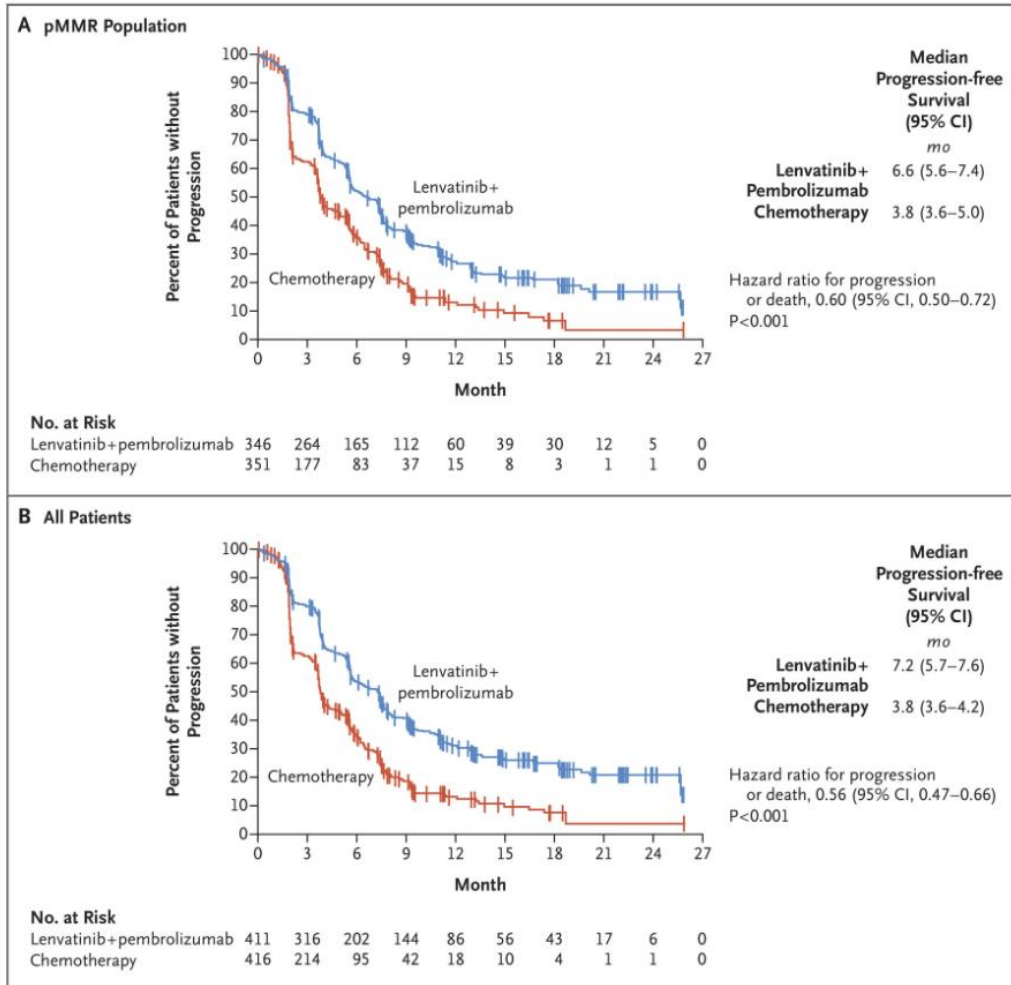
- As noted in paragraph 6.9, analysis of the dMMR subgroup in KN775 should be considered exploratory;
- KN158 was a relatively small phase 2 study;
- The comparison of a single arm study (KN158) with the comparator arm of another trial (KN775) was associated with a significant degree of bias. Without randomised allocation, there is a high risk of selection bias. The open label nature of the studies increased the risk of detection bias and the single arm study did not allow for any pre-specified statistical comparisons. Moreover, by using only one arm of the KN775 trial, any benefit associated with randomisation in KN775 was lost and patients between the two studies may not be comparable and unobserved confounders may exist due to the nature of the comparison;
- The submission did not provide an estimate of the incremental benefit of pembrolizumab monotherapy versus chemotherapy in dMMR patients.

**Progression free survival**

6.24 The submission stated that the PFS data presented in KN775 demonstrated that pembrolizumab and lenvatinib provides a clinically meaningful improvement for patients, reducing the risk of progression by 40% in the pMMR cohort (HR: 0.60 (95% CI: 0.50, 0.72) and by 44% in the ITT cohort (HR: 0.56 (95% CI: 0.47, 0.66).

6.25 The figures below present the Kaplan Meier curves for PFS in KN775 in the pMMR and all-comers populations.

Figure 2: KN775 Kaplan-Meier estimates of PFS in the pMMR and all-comer (ITT) populations



Source: Makker, V et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N Engl J Med 2022; 386:437-448  
CI = confidence interval; mo = months

- 6.26 The submission stated that the KN158 data demonstrated that for dMMR patients, pembrolizumab monotherapy may provide a comparable PFS benefit (13.1 months vs 10.7 months) to that observed with the combination therapy.
- 6.27 For the all-comers population and the pMMR cohort, the point estimate for the PFS HR does not meet the proposed MCID of PFS HR = 0.55. While the point estimate for the PFS HR in the dMMR cohort met the proposed MCID, the dMMR cohort was not part of the formal statistical analysis plan therefore results from this subgroup should be considered exploratory.

**Health related Quality of Life**

- 6.28 Health related quality of life (HRQoL), as measured by the global health status/quality of life (GHS/QoL) score from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ30), was a secondary outcome of the KN775 trial, whereas the EORTC QLQ-C30 physical functioning score EORTC QLQ-EN24 urological symptoms score, and the EQ-5D-5L VAS score were exploratory

endpoints. There were no patient reported outcomes or questionnaires included in any of the included single arm studies.

- 6.29 In KN775, there were no statistically significant differences between treatments in change from baseline in QLQ-C30 scores. The submission stated that there were no differences in the EORTC QLQ-C30 physical functioning scores, the EQ-5D, and the EORTC EN-24 urologic symptoms scores between the pembrolizumab plus lenvatinib arm and the chemotherapy arm.

### Comparative harms

- 6.30 Table 6 presents a summary of treatment related adverse events (TEAE) in KN775 in the all-comers population (i.e. including dMMR and pMMR patients).

**Table 6: Treatment Related Adverse Events (unadjusted) with combination therapy in KN775 all-comers population**

All Comers		KN775		Risk Difference (95% CI)	
		PEM+LEN (N=406) n (%)	Chemo (N=388) n (%)		
Patients with any TEAE <sup>a</sup>	Any TEAEs (one or more adverse events)	405 (99.8)	386 (99.5)	0 (-0.01, 0.01)	
	Treatment related TEAEs	395 (97.3)	364 (93.8)	0.03 (0.01, 0.06)	
	Severe TEAEs (CTCAE Grade 3 or above)	316 (77.8)	229 (59.0)	0.19 (0.12, 0.25)	
Patients with any serious AEs	Treatment-Emergent SAEs	135 (33.3)	55 (14.2)	0.19 (0.13, 0.25)	
	Deaths	6 (1.5)	8 (2.1)	-0.01 (-0.02, 0.01)	
TEAEs leading to study drug adjustment					
TEAEs leading to study drug interruption		281 (69.2)	105 (27.1)	0.42 (0.36, 0.48)	
		Lenva + Pembro	125 (30.8)	NA <sup>b</sup>	-
		Lenva	238 (58.6)		
		Pembro	203 (50.0)		
TEAEs leading to study drug reduction		270 (66.5)	50 (12.9)	0.54 (0.48, 0.59)	
		Lenva + Pembro	N/A	NA <sup>b</sup>	-
		Lenva	270 (66.5)		
		Pembro	N/A		
TEAEs leading to study drug withdrawal/discontinuation		134 (33.0)	31 (8.0)	0.25 (0.2, 0.3)	
		Lenva + Pembro	57 (14.0)	NA <sup>b</sup>	-
		Lenva	125 (30.8)		
		Pembro	76 (18.7)		
Selected Grade 3-5 Adverse Events					
Hypertension		154 (37.9)	9 (2.3)	0.36 (0.31, 0.41)	
Fatigue		21 (5.2)	12 (3.1)	0.02 (-0.01, 0.05)	
Diarrhoea		31 (7.6)	8 (2.1)	0.06 (0.03, 0.09)	
Weight decreased		42 (10.3)	1 (0.3)	0.1 (0.07, 0.13)	

*Public Summary Document – March 2022 PBAC Meeting with March 2023 Addendum*

Source: Table 2.5-13, p101 of the submission. Table 2.5-17, p107 of the submission

<sup>a</sup> A TEAE was defined as any adverse event that had an onset date, or a worsening in severity from baseline (pre-treatment), on or after the first dose of study drug up to 30 days following study drug discontinuation.

<sup>b</sup> Treatment not applicable to the chemotherapy arm

AE = adverse event; CI = confidence interval; LEN = lenvatinib; PEM = pembrolizumab; TEAE = treatment emergent adverse event.

- 6.31 Pembrolizumab plus lenvatinib was associated with a higher frequency of treatment emergent serious adverse events (TEAEs) compared with chemotherapy (33.3% versus 14.2%). The ESC noted that the ACM had commented that this increase in higher grade TEAEs was driven predominately by the inclusion of lenvatinib.
- 6.32 Pembrolizumab plus lenvatinib was associated with a higher incidence of Grade 3 or higher hypertension compared with TPC (37.9% versus 2.3%). The ACM commented that hypertension can be sudden onset and quite extreme. The ACM also noted the significant rate of gastrointestinal side effects.
- 6.33 In KN775, 66.5% of patients treated with lenvatinib required a dose reduction. Overall, the mean dose of lenvatinib in KN775 was 14 mg daily, compared with a starting dose of 20 mg daily.
- 6.34 The ESC considered that some of the adverse events associated with pembrolizumab plus lenvatinib were manageable, while others may be less manageable, noting that approximately one-third of patients discontinued pembrolizumab plus lenvatinib therapy due to TEAEs, compared with 8% in the TPC arm. The ESC considered that, in clinical practice, discontinuations and/or dose reductions (particularly of lenvatinib) may occur more frequently or earlier than observed in the trial, and this may impact effectiveness (i.e. the trial may overestimate the incremental effectiveness likely to be observed in clinical practice).
- 6.35 The submission argued that given the difference in exposure between the two arms, it was appropriate to adjust adverse events for time on treatment. This is presented in Table 7. The exposure adjusted TEAE results were used to inform the economic evaluation.

Table 7: Exposure adjusted grade 3-5 TEAEs for KN775 All-comers (ApaT population)

MedDRA System Organ Class Preferred Term	Event Count and Rate (Events/100person-months) <sup>a</sup>	
	Lenvatinib + Pembrolizumab	Chemotherapy
Number of participants exposed	406	388
Total exposure <sup>b</sup> in person-months	3919.5	1765.2
Blood and lymphatic system disorders	53 (1.4)	308 (17.4)
Anaemia	28 (0.7)	68 (3.9)
Febrile neutropenia	2 (0.1)	23 (1.3)
Leukopenia	0 (0.0)	43 (2.4)
Neutropenia	7 (0.2)	147 (8.3)
Gastrointestinal disorders	150 (3.8)	52 (2.9)
Diarrhoea	35 (0.9)	8 (0.5)
General disorders and administration site conditions	75 (1.9)	49 (2.8)
Asthenia	25 (0.6)	15 (0.8)
Fatigue	21 (0.5)	18 (1.0)
Hepatobiliary disorders	32 (0.8)	1 (0.1)
Infections and infestations	89 (2.3)	39 (2.2)
Investigations	214 (5.5)	281 (15.9)
Lipase increased	32 (0.8)	5 (0.3)
Neutrophil count decreased	10 (0.3)	159 (9.0)
Weight decreased	42 (1.1)	1 (0.1)
White blood cell count decreased	6 (0.2)	68 (3.9)
Metabolism and nutrition disorders	152 (3.9)	31 (1.8)
Decreased appetite	32 (0.8)	2 (0.1)
Hypokalaemia	22 (0.6)	6 (0.3)
Musculoskeletal and connective tissue disorders	34 (0.9)	5 (0.3)
Renal and urinary disorders	52 (1.3)	14 (0.8)
Proteinuria	22 (0.6)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	27 (0.7)	28 (1.6)
Skin and subcutaneous tissue disorders	36 (0.9)	3 (0.2)
Vascular disorders	221 (5.6)	16 (0.9)

Source: Table 2.5-21, p113 of the submission.

ApAT = All Patients as treated

<sup>a</sup> Event rate per 100 person-months of exposure = event count \*100/person-months of exposure.

<sup>b</sup> Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.

6.36 The ESC considered that the adjustment for exposure to treatment was not appropriate given that in practice these differences in time on treatment would also exist, and consequently these differences in risks of adverse events would be observed. Using increased exposure as a basis to change a safety claim may conflate time on treatment (which may largely be a factor of efficacy outcomes of PFS and OS) with safety. Additionally, given that the Grade 3 or higher adverse events may lead to changes in treatment (dose reductions, interruptions, discontinuations), it was unclear how to interpret the results of this analysis.

6.37 No comparative safety data for pembrolizumab monotherapy with doxorubicin or paclitaxel was presented. However, the PBAC has previously considered that a claim of superior safety for pembrolizumab monotherapy compared to paclitaxel or

docetaxel was supported in the consideration for pembrolizumab for treatment of patients with locally advanced or metastatic urothelial cancer after failure of a platinum-containing regimen (paragraph 7.7, p24-25 pembrolizumab public summary document (PSD) November 2017).

## Benefits/harms

6.38 Table 8 presents the summary of comparative benefits and harms of pembrolizumab in combination with lenvatinib compared to chemotherapy in the all-comers population. Because monotherapy claims were based on a non-comparative study this did not allow a quantitative comparison of benefits and harms for monotherapy.

**Table 8: Summary of comparative benefits and harms for pembrolizumab plus lenvatinib and doxorubicin or paclitaxel in the all-comers population (pMMR and dMMR)**

Benefits					
	PEM+LEN N=411	Chemo N=416	Absolute difference		HR (95% CI)
<b>Progression free survival</b>					
Progressed, n (%)	281 (68.4)	286 (68.8)			
Median (months)	7.2 (5.7, 7.6)	3.8 (3.6, 4.2)	3.4		<b>0.56 (0.47, 0.66)</b>
% progressed at 6 months (95% CI)	53.5 (48.4, 58.3)	34.3 (29.2, 39.4)	19.2%		
<b>Overall survival</b>					
Alive, n (%)	188 (45.7)	245 (58.9)			<b>0.62 (0.51, 0.75)</b>
Median (months)	18.3 (15.2, 20.5)	11.4 (10.5, 12.9)	6.9		
% alive at 12 months (95% CI)	62.5 (57.5, 67.1)	47.9 (42.7, 53.0)	14.6%		
<b>Harms</b>					
	PEM+LEN N=411	Chemo N=416	Event rate/100 patients*		RD (95% CI)
			PEM+LEN	Chemo	
TEAEs					
Grade 3 or above	316 (77.8)	229 (59.0)	78	59	0.19 (0.12, 0.25)
TEAEs leading to study drug withdrawal/ discontinuation	134 (33.0)	31 (8.0)	33	8	0.25 (0.2, 0.3)
Hypothyroidism	233 (57.4)	3 (0.8)	57	1	0.57 (0.52, 0.62)

Source: Table 2.5-2, p74 of the submission. Table 2.5-13, p101 of the submission; 11-5, p101 of KN775 CSR; Table 11-9, p111 of KN775 CSR

\*Median duration of follow-up: 12.2 months for pembrolizumab plus lenvatinib and 10.7 months for chemotherapy  
CI = confidence interval; HR = hazard ratio; PEM+LEN = pembrolizumab plus lenvatinib; RD = risk difference

6.39 On the basis of the KN775 trial presented in the submission, for every 100 patients treated with pembrolizumab plus lenvatinib (over a median follow up of 12.2 months) instead of chemotherapy (over a median follow-up of 10.7 months):

- 15 more patients were alive at 12 months; and
- 19 more patients were alive and progression free at 6 months.

6.40 On the basis of the KN775 trial presented in the submission, for every 100 patients treated with pembrolizumab plus lenvatinib (over a median follow up of 12.2 months) instead of chemotherapy (over a median follow-up of 10.7 months):

- Approximately 19 additional patients would have at least one adverse event of Grade 3 severity;
- Approximately 25 additional patients would have an adverse event leading to study drug withdrawal or discontinuation; and
- Approximately 57 additional patients would have hypothyroidism.

### ***Clinical claim***

#### **Combination therapy**

- 6.41 The submission claimed that for patients with advanced, recurrent or metastatic pMMR endometrial cancer who have failed at least one prior line of systemic platinum-based chemotherapy, pembrolizumab in combination with lenvatinib is superior in terms of comparative effectiveness and non-inferior in respect of exposure adjusted safety, when compared with doxorubicin or paclitaxel.
- 6.42 The ESC considered that the claim of non-inferior safety was not reasonable, as KN775 indicated that pembrolizumab plus lenvatinib was associated with inferior safety compared with chemotherapy. In particular, the ESC noted that pembrolizumab plus lenvatinib was associated with a higher frequency of TEAEs (33.3% versus 14.2%), and discontinuations due to TEAEs (33.0% versus 8.0%), along with Grade 3 or higher hypertension (37.9% versus 2.3%) and diarrhoea (7.6% versus 2.1%) compared with chemotherapy. Further, the ESC considered that the submission's adjustment for exposure may not have been appropriate and the adjustment of Grade 3 and above adverse events, which would be expected to lead to changes in treatment exposure made the results difficult to interpret.
- 6.43 The PBAC considered that the claim of superior efficacy of pembrolizumab plus lenvatinib was reasonable. The PBAC noted this benefit was observed in the ITT population (including both dMMR and pMMR patients) of KN775.
- 6.44 The PBAC considered the claim of non-inferior comparative safety was not adequately supported by the data. The PBAC considered that pembrolizumab plus lenvatinib has inferior safety versus chemotherapy given the toxicity associated with lenvatinib, but that the toxicity is manageable.

#### **Pembrolizumab monotherapy (dMMR)**

- 6.45 The PSCR claimed that for dMMR patients pembrolizumab monotherapy has superior efficacy and safety compared with doxorubicin or paclitaxel.
- 6.46 The quality of the evidence supporting pembrolizumab monotherapy was poor with only single arm studies available. Naïve side by side comparisons of the point estimates of OS in patients with dMMR tumours at landmark timepoints suggested an improvement in OS with pembrolizumab monotherapy (based on the single arm KN158 study) compared to chemotherapy (based on the chemotherapy arm of KN775 trial, dMMR subgroup). The ESC and the evaluation considered that a claim of superior efficacy for pembrolizumab monotherapy in patients with dMMR tumours was likely supported, however the magnitude of benefit was uncertain.

- 6.47 No comparative evidence was presented to support the claim of superior safety. The submission noted that the PBAC has previously considered that a claim of superior safety for pembrolizumab monotherapy compared to paclitaxel or docetaxel was supported in the consideration for pembrolizumab for treatment of patients with locally advanced or metastatic urothelial cancer after failure of a platinum-containing regimen (paragraph 7.7, p24-25 pembrolizumab PSD November 2017). The overall safety profiles of pembrolizumab and paclitaxel may be generally consistent between the two cancer types. Nonetheless, the ESC considered that a more conservative conclusion may be that pembrolizumab has a different adverse event profile (e.g. likely more immune related adverse events such as hyper/hypothyroidism) to chemotherapy (e.g. likely more haematological related adverse events such as anaemia and neutropenia).
- 6.48 The PBAC considered that the claim of superior comparative effectiveness of pembrolizumab monotherapy versus chemotherapy was not adequately supported, noting the data for pembrolizumab monotherapy was from a small single arm study.
- 6.49 The PBAC considered that the claim of superior comparative safety of pembrolizumab monotherapy versus chemotherapy was not adequately supported, noting that no comparative safety data was presented.

### ***Economic analysis***

- 6.50 The type of economic evaluation presented was a cost utility analysis. The submission did not present a stepped analysis. Table 9 presents the key components of the economic evaluation.
- 6.51 The submission applied only the publicly available list prices in the economic analysis and financial estimates (as outlined in Paragraphs 3.2 and 3.3). The sponsor requested that the PBAC make a recommendation on the basis of a net cost per patient. Given this approach, the following issues were noted:
- The submission conducted an analysis based on published list prices which resulted in an ICER of \$155,000 to < \$255,000 /QALY, which was not an accurate estimate of cost-effectiveness once effective prices are used.
  - The submission also presented a net cost per patient based on a specific ICER threshold (\$75,000 to < \$95,000/QALY gained, revised to \$75,000 to < \$95,000 /QALY in the pre-PBAC response). The ESC considered sensitivity analyses using multiple different ICER thresholds may be informative to better understand the sensitivity of the model to each of the key inputs, including over \$45,000 to < \$55,000 to \$55,000 to < \$75,000/QALY.
  - The use of a net cost per patient means that assumptions will be required to back-calculate the vial/unit price including assumptions around the total and relative utilisation of pembrolizumab (as combination in patients with pMMR or as monotherapy in dMMR) or lenvatinib, and the duration of therapy. The ESC noted that the model had used clinical data from KN775 and considered it was unclear

if the same durations of therapy and discontinuation rates would be observed in Australian clinical practice, for example discontinuation rates of lenvatinib may be higher in clinical practice.

- 6.52 The economic evaluation only modelled the Kaplan-Meier results of KN775 and the submission considered this was a conservative “proxy” for KN158 (pembrolizumab monotherapy study), given:
- The ITT results of KN775 (HR=0.62) are driven by that of the dMMR subgroup (HR=0.37), which contributed 15.7% of the total trial population. The submission further argued that dMMR patients may contribute up to 31% of the potential PBS population; and
  - Modelling KN158 would require a matching adjusted indirect comparison (MAIC) to the dMMR chemotherapy arm of KN775. Inherent limitations of the MAIC aside, the submission argued that the results would be favourable to pembrolizumab given the larger difference in survival outcomes between pembrolizumab and chemotherapy in dMMR patients (i.e., a larger difference than observed in the ITT population).
- 6.53 The evaluation and the ESC considered that it was unclear if this was a conservative approach as the submission had not provided sufficient evidence that pembrolizumab monotherapy in the dMMR subgroup has comparable incremental efficacy to pembrolizumab and lenvatinib in the all-comers population. Because the economic evaluation only included data from the KN775 trial of pembrolizumab plus lenvatinib and given the lack of evidence presented to quantify the incremental effectiveness of pembrolizumab monotherapy versus chemotherapy, the evaluation and the ESC considered that the cost-effectiveness of pembrolizumab in the monotherapy setting was unclear.
- 6.54 The model used the ITT results from KN775, rather than the results from the pMMR subgroup. Sensitivity analyses indicated that the ICER increased by 9% when the pMMR subgroup results were used. The PBAC considered use of the ITT results in the model was appropriate given: as outlined in paragraph 7.8, it had advised that the restriction should allow use of combination therapy in all patients regardless of biomarker status; and there was no evidence of biomarker status being a treatment effect modifier.

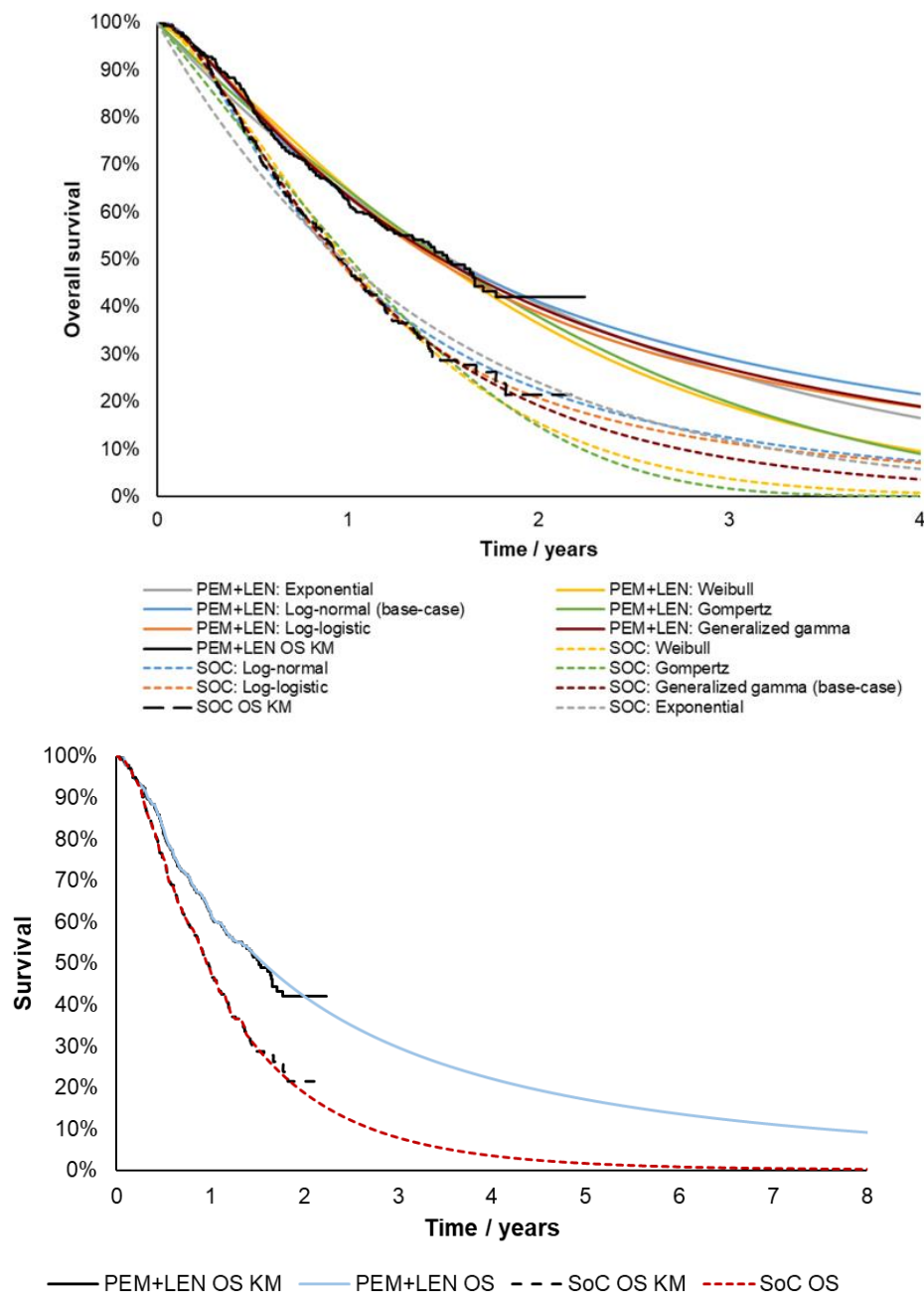
**Table 9: Key components of the economic evaluation**

Component	Description
Type of analysis	CUA
Treatment comparison	Intervention: pembrolizumab plus lenvatinib Comparator: chemotherapy (doxorubicin or paclitaxel – informed by KN775)
Patient population	Aligned with the KN775 trial ITT population.
Outcomes	Quality-adjusted life years; life-years
Time horizon	10 years, based on 11.4 months median follow-up in the KN775 trial. Revised to 8 years in the PSCR and 5 years in the pre-PBAC response.
Methods used to generate results	Partitioned survival analysis
Health states	Progression free, progressed disease, death
Cycle length	1 week, no half-cycle correction
Allocation to health states	Allocation to health states was based on the Kaplan-Meier estimates for PFS and OS in KN775. The trial-based survival estimates were used up until 72.6 weeks for PFS and OS in both treatment arms in the base case analysis. Treatment duration was modelled using time on treatment data from KN775.
Extrapolation	Base case: 1 piece model with parametric extrapolations Alternate base case: Piecewise parametric extrapolation
Health related quality of life	EQ-5D scores from KN775 were used to derive utility estimates based on an Australian scoring algorithm PFS health state utility: 0.736 for both arms PD health state utility: 0.700 for both arms The plausibility of the health state utilities being so similar for progression free and progressed health states was unclear. However, the increment was somewhat similar to the only other identified economic evaluation that relied on endometrial cancer trial based utilities (Thurgar 2018: 0.817 and 0.779 for progression free and progressed, respectively, based on analyses of EQ-5D data within KN158 for women with dMMR/MSI-H mEC and based on a US algorithm). The model was moderately sensitive to the source of the utility estimates, and the base case estimate was the more conservative of the two.
Software package	Excel 2010

Source: Table 3.1-1, pp134-135 of the submission. CUA = cost-utility analysis; EQ-5D = EuroQoL 5 dimensions; OS = overall survival; PD = progressive disease; PFS = progression free survival; QALY = quality-adjusted life year;

- 6.55 The extrapolation of OS and PFS for pembrolizumab plus lenvatinib and chemotherapy were modelled independently. Standard one-piece models were fitted to the data in the base-case to align with PBAC preferences, however demonstrated poor visual and statistical fit. Therefore, the submission presented an alternate base-case in which piecewise models were fitted to the data.
- 6.56 The submission applied different functions in each arm for modelling OS and PFS (in both the standard parametric extrapolations and the flexible piecewise models). The use of independent modelling of each arm was done in order to model an assumed survival plateau associated with immunotherapy.
- 6.57 Figure 3 presents the OS one-piece parametric extrapolations explored by the submission. In the base case, the submission chose the log-normal function for the pembrolizumab plus lenvatinib arm (light blue solid line on the figure below), and the generalised gamma function for the chemotherapy arm (red dotted line).

Figure 3: (A) OS one-piece parametric survival curves for PEM+LEN vs. chemotherapy (B) base case of submission



Source: Figure 3.4-1, p147 of the submission. KM, Kaplan–Meier; OS, overall survival; SoC, standard of care

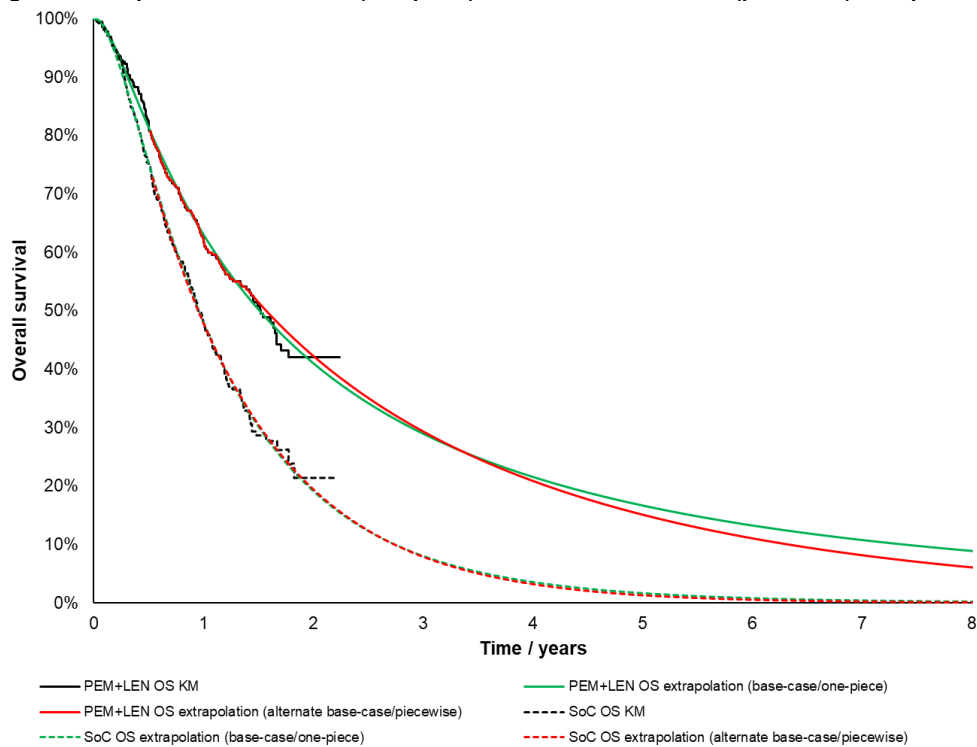
6.58 The PSCR reiterated the choice of the log-normal (best visual and statistical fit for pembrolizumab plus lenvatinib) and the generalised gamma (best visual fit for chemotherapy) functions, stating that using the log-logistic function in the chemotherapy arm (best statistical fit based on AIC and BIC) would “result in clinically implausible outcomes, given the well documented poor survival of chemotherapy patients.” The ESC noted that the independent modelling of each arm was used in order to model a survival plateau associated with immunotherapy, but considered

that such a plateau was not clearly demonstrated in the KN775 trial, given the relatively short duration of follow-up. The pre-PBAC response maintained that the original extrapolations provided the most clinically plausible outcomes, but provided a revised model using the best-fitting extrapolation functions for OS (log-normal for pembrolizumab plus lenvatinib; log-logistic for chemotherapy).

**Flexible piecewise model (alternate base case)**

- 6.59 The submission also provided an alternate base-case in which flexible piecewise models were fitted to the data. The submission used a cut-off at Week 26 based on structural changes observed in the Chow tests for OS for the pembrolizumab plus lenvatinib arm of KN775 (ITT). For consistency, a cut-off at Week 26 was also selected for the chemotherapy arm. The ESC considered the selection of Week 26 as the cut-off point was appropriate.
- 6.60 The PSCR updated the extrapolation functions for OS to those with the best statistical fit (based on AIC and BIC), which were Weibull for pembrolizumab plus lenvatinib and exponential for chemotherapy. This change was conservative (in the PSCR’s analysis which used an ICER threshold of \$75,000 to < \$95,000/QALY) and meant that the alternate base-case resulted in a lower cost per patient than the one-piece model.
- 6.61 The figure below compares the piecewise model and the one-piece model using the PSCR extrapolations.

**Figure 4: Comparison of base case (one-piece) and alternate base case (piecewise) extrapolation**



Source: Attachment 3.1 - CEM PEM+LEN previously treated advanced EC\_PBAC\_Nov21\_FINAL\_PSCR

- 6.62 The ESC noted an assumption underpinning the use of piecewise models is that the data within each section is sufficient for robust survival modelling (NICE DSU paper 21, 2020). The ESC noted that, in general, splitting a single set of data into sections according to time means that sample sizes are reduced in later segments of the curve, where patient numbers at risk may be small and the number of observed events may be low, which may lead to large standard errors and uncertainty when fitting survival models. The ESC considered that the submission and PSCR had not provided adequate information regarding the sample size, particularly in the second section of the two-piece model with the Weibull function applied.
- 6.63 In particular, the ESC noted that the piecewise extrapolation resulted in additional weight being attached to the tail of the Kaplan-Meier data i.e., the extrapolation is more sensitive to survival data informed by lower patient numbers.
- 6.64 The submission stated the piecewise approach was selected to represent an assumed plateau in survival. However, the ESC considered that modelling a survival plateau may not be supported by the clinical evidence presented in the submission given the relatively short duration of follow-up and immature OS data.
- 6.65 Table 10 presents the key drivers of the model presented in the submission.

**Table 10: Key drivers of the submission's model**

Description	Method/Value in submission base case	Impact on one-piece model
Extrapolation	Parametric functions were fitted to the trial data to extrapolate respective survival curves to the model time horizon. In the base case analysis of the submission, 74.7% of the incremental QALYs and 11.4% of incremental costs were generated beyond year 2 (i.e. the approximate extrapolation time point for OS).	High, favours pembrolizumab + lenvatinib. In the base case, if the chemotherapy arm extrapolation employed the best fitting parametric curve, the ICER would increase by 16%. The pre-PBAC response proposed a revised base case that used the best-fitting parametric curves.
Time horizon	10 years in the submission.	High, favours pembrolizumab + lenvatinib. Reducing time horizon to 5 years increases ICER by 31%. The pre-PBAC response revised the time horizon to 5 years.
Time on pembrolizumab treatment truncation	2 years, consistent with requested restriction but not KN775.	Moderate to high, favours pembrolizumab lenvatinib. Removing truncation increases the ICER by 14%

Source: pp134-139 of the submission.

- 6.66 The submission used a 10 year time horizon, which was shortened to 8 years in the PSCR. The PSCR stated that these time horizons were supported by “the magnitude of OS gain observed in KN775, the longer term sustained benefit observed in KN158, and the durable response observed with immunotherapies”. However, the ESC considered that a 5 year time horizon may be more appropriate given the aforementioned uncertainties with the extrapolation and also given the population of pMMR patients in the second- or later-line setting. The revised analysis in the pre-PBAC response applied a 5 year time horizon.

6.67 The submission conducted an analysis based on published list prices which resulted in an ICER of \$155,000 to <\$255,000 /QALY, however this does not accurately reflect the ICER once effective prices are used. Thus Table 11 and Table 12 present the results of the economic evaluation using the net cost per patient to achieve an ICER of \$75,000 to < \$95,000/QALY gained. These tables are based on the revised scenario proposed in the pre-PBAC response which incorporated a 5 year time horizon, a \$75,000 to < \$95,000/QALY threshold and use of the best-fitting parametric curves (i.e. updating the chemotherapy arm extrapolation to log-logistic in the one-piece model). Table 11 presents the revised base case (one-piece extrapolation) while Table 12 presents the alternative base case economic evaluation (piecewise extrapolations).

**Table 11: Results of the economic evaluation (base case) presented in the pre-PBAC response to achieve an ICER of \$75,000 to < \$95,000/QALY**

Component	PEM + LEN	Chemo	Increment
Costs (\$)		\$55,923	
LYs	2.01	1.32	0.70
QALYs	1.45	0.94	0.50
<b>Incremental cost/extra QALY gained (base case in pre-PBAC response) (\$)</b>			<b>1</b>
<b>Net cost per patient (undiscounted) proposed in pre-PBAC response (\$)</b>			
Net cost per patient (undiscounted) proposed in PSCR (\$)			

Source: "Controls" worksheet of "Endometrial cancer Section 3 model.xlsx"

LEN = lenvatinib; LY = life-year; PEM = pembrolizumab; QALY = quality adjusted life-year.

Blue shading indicates cost per patient proposed in PSCR

The redacted values correspond to the following ranges:

<sup>1</sup> \$75,000 to < \$95,000

**Table 12: Results of the alternative base case (piecewise extrapolations) presented in the pre-PBAC response to achieve an ICER of \$75,000 to < \$95,000/QALY**

Component	PEM + LEN	Chemo	Increment
Costs (\$)		\$57,549	
Lys	2.00	1.23	0.77
QALYs	1.44	0.88	0.56
<b>Incremental cost/extra QALY gained (alternate base case in pre-PBAC response) (\$)</b>			<b>1</b>
<b>Net cost per patient (undiscounted) proposed in pre-PBAC response (\$)</b>			
Net cost per patient (undiscounted) proposed in PSCR (\$)			

Source: "Controls" worksheet of "Endometrial cancer Section 3 model.xlsx"

LEN = lenvatinib; LY = life-year; PEM = pembrolizumab; QALY = quality adjusted life-year.

Blue shading indicates cost per patient proposed in PSCR

The redacted values correspond to the following ranges:

<sup>1</sup> \$75,000 to < \$95,000

6.68 As shown in the tables above, in the pre-PBAC response revised scenarios, the undiscounted cost per patient was \$1 in the base case (and \$1 in the alternative base case). The PBAC noted that this was lower than offered in the submission (\$1), and PSCR (\$1) was the lowest cost offered in the PSCR, which was based on the piecewise extrapolation alternative base case).

6.69 Sensitivity analyses were calculated during the evaluation using hypothetical effective prices for pembrolizumab and lenvatinib to achieve the proposed \$75,000 to < \$95,000 ICER. The ESC also conducted analyses using a \$55,000 to < \$75,000/QALY ICER threshold. The same percent rebate (1%) was applied to each drug in order to

incorporate the impact of the underpinning assumptions such as the duration of use of each component. The sensitivity analyses on the base case (one-piece extrapolation) from the PSCR model are presented in Table 13 based on these hypothetical prices. This table also presents a percent change to the ICER/QALY (noting the absolute value is not presented as it is not meaningful when published prices are used). Note that the cost per patient is based on discounted costs (rather than undiscounted costs, as used in the preceding tables).

**Table 13: Sensitivity analyses based on PSCR one-piece base case, 8 year time horizon**

Analyses	% change to ICER with published prices	Cost per patient based on ■ <sup>1</sup> /QALY threshold (\$)	Cost per patient based on ■ <sup>2</sup> /QALY threshold (\$)
<b>Base case</b>	0%		
<b>Univariate sensitivity analyses</b>			
Time horizon 5 years (vs 8 in PSCR)	+31%		
<b>Terminal care costs (base case: \$51,413)</b>			
Terminal care costs removed	+4%		
Terminal care costs halved	+2%		
<b>OS extrapolation (base case: PEM+LEN = log-normal; chemotherapy = gen-gamma)</b>			
Best fitting curve for OS for chemotherapy arm (log-logistic)	+16%		
Log normal in both arms	+15%		
Generalised Gamma in both arms	+13%		
<b>Patient population modelled (base case: based on KM curves from ITT population of KN775)</b>			
pMMR patients (i.e. using the pMMR subgroup from KN775)	+9%		
<b>Utilities (base case: 0.736 in PFS; 0.70 in PD health state based on KN775)</b>			
Use Thurgar (2018) utilities (KN158) PFS: 0.817; PD: 0.779	-10%		
10% lower utility in progressed disease health state	+5%		
<b>Other</b>			
No lenvatinib ToT truncation	+3%		
No pembrolizumab ToT truncation	+14%		
Discount rate 0% (vs 5%)	-12%		
Discount rate 3.5% (vs 5%)	-4%		
<b>Multivariate sensitivity analyses</b>			
5 year time horizon + pMMR subgroup	+41%		
5 year time horizon + terminal care costs removed	+38%		
5 year time horizon + terminal care costs removed + pMMR subgroup	+48%		
Best fitting curve for chemotherapy for OS + terminal care costs removed + pMMR subgroup	+36%		

Source: Model settings sheet of 'Attachment 3.1 - CEM PEM+LEN previously treated advanced EC\_PBAC\_Nov21\_FINAL\_PSCR.xlsx'. ICER = incremental cost effectiveness ratio; LEN = lenvatinib; OS = overall survival; PEM = pembrolizumab; PFS = progression free survival; ToT = time on treatment

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$75,000 to < \$95,000

6.70 The model was sensitive to the extrapolation method for overall survival and the time horizon.

- 6.71 The model was moderately sensitive to removing pembrolizumab time on treatment truncation. The model assumed that all patients discontinued pembrolizumab at two years, in line with the proposed restriction, but as described in paragraph 6.10, 9% of patients in the pembrolizumab plus lenvatinib arm in KN775 remained on treatment after week 104.
- 6.72 The model was also moderately sensitive to the inclusion of terminal care costs. Terminal care costs (\$51,413) were based on Goldsbury 2018. However, the ESC noted that these costs were averages of several kinds of cancers, of which none were endometrial. It is unclear whether this average would be representative of endometrial cancer costs. Further, the ESC noted that the terminal care cost was based on the 12 months prior to death and considered this may result in double counting as some of these costs would have accrued in the progressed health state.
- 6.73 Given that there is no indication-specific clinical evidence to support that pembrolizumab plus lenvatinib would improve survival in the long term, and the issues with the cost estimate itself, the ESC considered that it is likely more reasonable to assume that there would be no difference in terminal care costs between the treatment arms, or that a small difference may accrue due to the impact of discounting. The ESC noted the impact of including terminal care costs on the ICER is driven by the difference in surviving proportions at the end of the model time horizon but ultimately this cost should accrue to all patients in both treatment arms.

## Drug cost/patient

- 6.74 The drug cost per patient for pembrolizumab and lenvatinib are outlined in Table 14.

**Table 14: Drug cost per patient for pembrolizumab and lenvatinib (pre-PBAC response)**

Drug	Number of administrations			Total cost per course	
	KN775	Model	Financial	Model (\$)	Financials (\$)
<b>Pembrolizumab plus lenvatinib</b>					
Pembrolizumab	12.1	<sup>a</sup>	<sup>b</sup>	\$	\$
Lenvatinib	8.4 "months"	<sup>c</sup> months" at dose intensity	<sup>d</sup> months at dose of mg		
Total					
<b>Chemotherapy</b>					
Doxorubicin	4.8	5.2	17.33	\$	\$
Paclitaxel	6.7	12.7	17.33	\$	\$
Total				\$	\$

Source: Table 3.8-1, p178 of the submission and "endometrial cancer Section 3 model.xlsx" Table 10-7, p90 of KN775 CSR, and 'Endometrial cancer Section 4 Workbook – Revised.xlsx'

Note: small discrepancies between presented results and products of their presented factors are due to rounding.

<sup>a</sup> based on column BH of worksheet 'PF – PEM + LEN', including the submission's assumption of 100% dose intensity.

<sup>b</sup> based on mean treatment duration of weeks (per PSCR) divided by one administration every 3 weeks.

<sup>c</sup> based on column BI of worksheet 'PF – PEM + LEN', including the submission's assumption of % dose intensity. One "month" is 30 days to align with the lenvatinib pack size.

<sup>d</sup> based on the figure stated in the PSCR and pre-PBAC response; however the figure that appeared to be applied was

<sup>e</sup> weighted average 25.47% paclitaxel vs 74.53% doxorubicin use

### Estimated PBS usage & financial implications

6.75 The submission was considered by DUSC. The submission used an epidemiological approach to estimate utilisation. The submission estimated incident patients in all years and a prevalent pool of patients in the first year. The incident patients included two pools of patients, patients initially diagnosed with advanced (Stage III or IVa) or metastatic (unresectable, Stage IVb), and patients who have had a distant recurrence from earlier stages I or II endometrial cancer that is not amenable to local therapy (surgery or radiation) with curative intent.

6.76 Data sources used for estimating the financial implications are presented in Table 15.

**Table 15: Data sources and parameter values applied in the utilisation and financial estimates**

Data	Value	Source	Comment
<b>Eligible population</b>			
Incident uterine patients	█ <sup>1</sup> in Year 1 increasing to █ <sup>1</sup> in Year 6	AIHW 2021	The submission did not describe the extrapolation but appeared to use a 2%-2.6% growth rate from 2021 onward.
% incident uterine patients who have endometrial cancer	95%	Cancer Council	This source could not be verified from the information provided in the submission.
<b>Applied to both incident cohorts (those initially diagnosed with advanced/metastatic and distant recurrence)</b>			
% patients treated first line	70%, increased to 75% in pre-PBAC response	Assumption	DUSC considered 70% was reasonable. Despite this, the pre-PBAC response increased the proportion of patients receiving 1L treatment to 75% to allow for 5% more patients to initiate 1L therapy in order to receive 2L treatment (mostly dMMR patients). PBAC considered this increase may not be reasonable.
% patients eligible for second line	49%	Based on 51% response rate in Miller (2012) RCT	DUSC considered this estimate may be reasonable.
% ECOG 0-1	80%, increased to 83% in pre-PBAC response	Assumption	DUSC considered this was reasonable. However, the pre-PBAC response increased this to 83% to allow eligibility for an estimated 15% of dMMR patients with ECOG 2. PBAC considered this increase may not be reasonable given the listing restricted use to patients with ECOG 0-1.
<b>Patients initially diagnosed with advanced or metastatic disease</b>			
% patients with advanced or metastatic cancer at diagnosis	18%, reduced to 10% in the pre-PBAC response	SEER database	DUSC considered that a proportion of Stage III patients would be treated with curative intent and should be added to the estimate of the number of Stage I and II patients. Thus, the pre-PBAC response removed 8% of advanced/metastatic population (approximately 90% of Stage III patients were assumed to be resectable based on clinician feedback).
<b>Patients who had a distant recurrence from Stages I or II endometrial cancer that is not amenable to local therapy with curative intent</b>			

Public Summary Document – March 2022 PBAC Meeting with March 2023 Addendum

Data	Value	Source	Comment
% with Stage I or II at diagnosis	82%, increased to 90% in pre-PBAC response	SEER database	Refer to row above “% patients with advanced or metastatic cancer at diagnosis”.
% Patients with distant recurrence from earlier stages	12.5%	19.5% recurrence rate x 64% distant recurrence (Vizza 2020)	DUSC considered this proportion was likely underestimated as patients would be eligible for second line treatment if they were considered not to be suitable for curative treatment, rather than only if they had distant recurrence.
% patients with distant recurrence and alive	95%, increased to 100% in pre-PBAC response	Assumption	DUSC considered this was inappropriate and should be removed, as the step estimating the proportion eligible for second line treatment accounts for patients who do not survive.
<b>Prevalent pool</b>			
1 Year overall survival	92.5%, reduced to 83.5% in pre-PBAC response	AIHW data visualisations	DUSC noted 92.5% is based on the % of patients who survive 1 year after diagnosis and considered that as the prevalent pool were not all diagnosed in the last year, it was not reasonable to apply the 1 year OS rate to all prevalent patients. The pre-PBAC response estimate of 83.5% was based on the 5-year relative survival from the AIHW data.
<b>Treatment utilisation</b>			
% assumed to received lenvatinib	87%, reduced to 85% in PSCR and 75% in pre-PBAC response		DUSC considered it was unclear how this has been applied and that the estimate of the proportion pMMR may be overestimated. PBAC considered the proportion of patients who would initiate lenvatinib may be higher given its advice to allow use of combination therapy in all-comers.
Uptake rate of pembrolizumab plus lenvatinib	95%	Assumption	DUSC considered this was reasonable
Current uptake rate of second line chemo	60% will use chemo, of which 75% use doxorubicin and 25% use paclitaxel	Assumption	
Pembrolizumab administrations per patient	█	Updated in PSCR based on █ weeks mean duration from economic model, divided by 3 (three weeks)	The economic model estimated █ administrations per patient.
Lenvatinib administrations per patient	█ 10mg scripts █ 4mg scripts <sup>a</sup>	The submission stated this was based on the economic evaluation, however this could not be verified.	A dose intensity of █% for lenvatinib was assumed in the economic evaluation, which was roughly consistent with the financial estimates (20mg x █% = █ mg)
<b>Costs</b>			
MBS costs	\$112.40	13950 Parenteral administration of one or more antineoplastic agents	Reasonable.

Public Summary Document – March 2022 PBAC Meeting with March 2023 Addendum

Data	Value	Source	Comment
<b>Grandfather patients</b>			
Grandfather patients	50 patients	Assumption	The submission estimated there would be 50 grandfathered patients, who were assumed to already be included in the prevalent patient population. The pre-PBAC response outlined that these grandfather patients would receive 50% of the time on treatment.

Source: pp191-208 of the submission. AIHW = Australian Institute for Health and Wellness; dMMR = deficient mismatch repair; MBS = Medicare Benefits Schedule; mg= milligram; PBS = Pharmaceutical Benefits Scheme; pMMR = proficient mismatch repair;

<sup>a</sup> As stated in the PSCR, however the figure that appeared to be applied was [REDACTED].

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5000

- 6.77 The submission did not explicitly calculate the cost of pembrolizumab monotherapy, but factored in estimates of the proportion of patients with dMMR to calculate the number of lenvatinib scripts. The submission assumed that of the available patient pool, 16% of patients will be dMMR and 84% pMMR, based on the proportion in the KN775 study. The submission had originally assumed that 20% of dMMR patients would use combination therapy (with the remaining 80% using monotherapy) as the proposed TGA restriction at the time of the submission allowed use of combination therapy in dMMR patients. The pre-PBAC response revised the proportion of patients receiving lenvatinib to 75%, however the basis for this was unclear. The PBAC considered that the proportion of patients who initiate lenvatinib may be higher than 75%, and close to 100%, given its advice that the restriction should allow use of combination therapy in all-comers.
- 6.78 The PBAC noted that the financial estimates assumed the average dose of lenvatinib would be 14 mg per patient (i.e. a relative dose intensity for lenvatinib of around 70%, consistent with the economic model) based on the ITT population in KN775.
- 6.79 The submission presented two sets of financial estimates. One approach relied on published prices (for the reasons outlined in Paragraphs 3.2 and 3.3), and thus does not reflect the expected costs to the PBS once effective prices are applied. The other approach (which was the only approach presented in the pre-PBAC response) was based on a simple multiplication of the estimated number of patients and the net cost per patient. While the estimates derived from the latter approach were more indicative of the expected costs once effective prices are applied (and are presented in Table 16), they do not account for factors such as: part-treatment costs in grandfather patients; offsets for chemotherapy; and MBS costs. The PBAC noted these issues would need to be addressed.
- 6.80 Table 16 outlines the pre-PBAC response’s estimate of the financial implications of listing pembrolizumab in combination with lenvatinib using the proposed cost per patient of \$[REDACTED]. A number of changes to the financial estimates were proposed in the pre-PBAC response (outlined in Table 15 above), however the resulting number of patients treated per year could not be replicated (i.e. when the changes stated in the

pre-PBAC response were applied to the worksheet submitted with the PSCR) and thus the pre-PBAC response estimates have not been verified.

**Table 16: Indicative cost of listing pembrolizumab + lenvatinib**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Net financial implications (stated in pre-PBAC response; not able to be replicated)</b>						
Treated initiating patients	1	1	1	1	1	1
Net cost to PBS/RPBS (\$)	2	2	2	2	2	2
<b>PSCR</b>						
Treated patients	1	1	1	1	1	1
Net cost to PBS/RPBS (\$)	3	3	3	3	3	3

Source: Page 3 of the pre-PBAC response, Page 6 of the DUSC advice. PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

Blue shading indicates cost per patient proposed in PSCR.

The redacted values correspond to the following ranges:

<sup>1</sup>< 500

<sup>2</sup>\$10 million to <\$20 million

<sup>3</sup>\$20 million to <\$30 million

6.81 DUSC considered the estimates presented in the submission to be slightly overestimated. The main issues were:

- The submission’s estimates of the patient population may be reasonable, but the paucity of strong epidemiological data in the Australian context made the estimates uncertain.
- As with the economic evaluation, the submission’s estimates relying on published prices are not reflective of expected costs to the PBS and to government.
- A proportion of Stage III patients would be treated with curative intent and should be added to the estimate of the number of Stage I and II patients. The pre-PBAC response addressed this by reducing the percent of advanced/metastatic patients from 18% to 10%, and commensurately increasing the proportion of patients with recurrent disease from 82% to 90%. The PBAC considered this was appropriate.
- It was unclear how the estimated proportion of patients with pMMR was applied in the PSCR (refer to Paragraph 6.77).

6.82 The PBAC noted that a number of changes to the financial estimates were proposed in the pre-PBAC response (as outlined in Table 15) and considered that the following two changes were not appropriate: (a) increasing the proportion of patients treated first line (from 70% to 75%); and (b) increasing the proportion of patients with ECOG 0 or 1 (from 80% to 83%). The PBAC noted that DUSC had considered that the original estimates for these two parameters were reasonable.

### **Financial Management – Risk Sharing Arrangement**

6.83 The submission stated that the sponsor is willing to enter into a risk sharing arrangement (RSA).

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

## 7 PBAC Outcome

### Pembrolizumab plus lenvatinib (combination therapy)

- 7.1 The PBAC recommended the listing of pembrolizumab for use in combination with lenvatinib for the treatment of patients with advanced endometrial cancer who have disease progression following prior systemic therapy regardless of biomarker status on the basis that it should be available only under special arrangements under Section 100 (Efficient Funding of Chemotherapy). The PBAC was satisfied that pembrolizumab plus lenvatinib provides, for some patients, a significant improvement in efficacy including an improvement in overall survival (OS) compared with chemotherapy. The PBAC noted this clear benefit was observed in all-comers in the key trial (KN775) regardless of biomarker status. The PBAC considered that pembrolizumab plus lenvatinib would be cost-effective at the cost per patient proposed in the pre-PBAC response based on the one-piece model.
- 7.2 The PBAC considered there is a high unmet need for effective therapies to treat this condition, noting immunotherapies have been the first major advance in endometrial cancer treatment for many years.
- 7.3 The PBAC considered the nominated comparator, chemotherapy (comprising doxorubicin or paclitaxel), was appropriate.
- 7.4 The PBAC considered that the claim of superior efficacy of pembrolizumab plus lenvatinib versus chemotherapy, based on the results of the comparative KN775 trial, was reasonable. The PBAC noted that the superior efficacy was observed in the ITT population comprising both dMMR and pMMR patients, with a substantial OS gain observed (ITT HR: 0.62 (95% CI: 0.51, 0.75)), and a 6.9 month increase in median survival (18.3 versus 11.4 months).
- 7.5 The PBAC noted that the TGA ACM had 'expressed disappointment that the design of the KN775 trial did not allow efficacy in dMMR patients to be specifically analysed'. Patients with dMMR tumours comprised 15.7% of the total trial population, and subgroup analyses of the dMMR population were not included in the pre-specified statistical analysis plan and were thus considered exploratory. The PBAC noted that the TGA had not registered combination therapy with pembrolizumab plus lenvatinib in the dMMR population, with the ACM advising that 'single agent pembrolizumab is an effective option for patients with dMMR advanced endometrial cancer, without the added toxicity from lenvatinib in the combination therapy'. However, as outlined above, the PBAC noted that in KN775 the superior efficacy of combination therapy was observed in the ITT population comprising both dMMR and pMMR patients with no evidence that biomarker status was a treatment effect modifier. The PBAC noted that the HR for OS was 0.68 (95% CI: 0.56, 0.84) in the pMMR subgroup and 0.37 (95%

- CI: 0.22, 0.62), in the dMMR subgroup, but acknowledged the latter estimate was based on an exploratory analysis.
- 7.6 The PBAC considered that, given the design of the study, the efficacy contribution of each agent in the combination could not be determined. In particular, the PBAC considered that it was unable to conclude that lenvatinib offers no benefit in the dMMR population. While lenvatinib is associated with increased toxicities, these are generally predictable and manageable.
- 7.7 The PBAC considered that claim of non-inferior comparative safety was not adequately supported by the data. The PBAC noted that pembrolizumab plus lenvatinib was associated with a higher incidence of Grade 3 or higher hypertension (37.9% versus 2.3%, respectively) and diarrhoea (7.6% versus 2.1%) and considered these were driven predominately by the inclusion of lenvatinib. The PBAC considered that pembrolizumab plus lenvatinib has inferior safety versus chemotherapy given the toxicity associated with lenvatinib, but that this toxicity is often manageable with dose reductions or interruptions. In some cases, discontinuation of lenvatinib is required (with 30.8% of patients in KN775 ceasing lenvatinib due to toxicity). The PBAC considered that oncologists are familiar with managing lenvatinib toxicity, and that the restriction should allow clinicians flexibility to cease lenvatinib (but continue pembrolizumab as a single agent) in the event of toxicity or to use pembrolizumab as a single agent in patients in whom lenvatinib is contraindicated.
- 7.8 Overall, the PBAC considered that combination therapy with pembrolizumab plus lenvatinib has an acceptable risk-benefit profile for the all-comer population, regardless of biomarker status. As such, the PBAC recommended that the restriction should allow use of combination therapy in both pMMR and dMMR patients; but, as above, allow use of single-agent pembrolizumab in patients who experience toxicity with lenvatinib or in whom lenvatinib is contraindicated.
- 7.9 The submission presented a cost-utility analysis of pembrolizumab plus lenvatinib versus chemotherapy. The PBAC noted that the economic evaluation only modelled the Kaplan-Meier results from KN775 (combination therapy), and did not specifically assess the cost-effectiveness of pembrolizumab monotherapy versus chemotherapy. Further, the KN775 results applied in the model were from the ITT population. The PBAC considered use of the ITT results in the model was appropriate given: as outlined in paragraph 7.8, it had advised that the restriction should allow use of combination therapy in all patients regardless of biomarker status; and there was no evidence of biomarker status being a treatment effect modifier.
- 7.10 The PBAC noted that lenvatinib and pembrolizumab are each marketed by different companies, and that the submission had not proposed a specific price per pack of lenvatinib or per vial of pembrolizumab. Instead, the submission requested that the PBAC make a recommendation on the basis of a net cost per patient, back-calculated using a specific ICER threshold (\$75,000 to < \$95,000/QALY gained, revised to \$75,000 to < \$95,000/QALY in the pre-PBAC response).

- 7.11 The base case of the economic evaluation used standard one-piece parametric models to extrapolate survival. The PBAC noted that the submission also provided an “alternate base-case” in which flexible piecewise extrapolation models were fitted to the data. The submission stated this approach was selected to represent an assumed plateau in survival, however, the PBAC considered that a survival plateau was not adequately supported by the clinical evidence presented in the submission given the relatively short duration of follow-up and immature OS data (median follow-up was 11.4 months in KN775). Further, the PBAC agreed with the ESC that the use of a two-piece extrapolation method resulted in additional weight being attached to the tail of the Kaplan-Meier data (where patient numbers are low and the data is less reliable) and considered that a one-piece extrapolation method fitted to the full KM curve was more reliable.
- 7.12 The pre-PBAC response provided a revised economic model that used a 5 year time horizon, the best-fitting parametric extrapolation in all arms, and an ICER threshold of \$75,000 to < \$95,000/QALY, which resulted in a net cost per patient of \$1 (using the one-piece extrapolation). The PBAC considered that these changes adequately addressed the concerns raised by the evaluation and ESC regarding the extrapolation approach used in the submission and PSCR. The PBAC considered that pembrolizumab plus lenvatinib would be acceptably cost-effective using the parameters outlined in the pre-PBAC response with the one-piece extrapolation.
- 7.13 The PBAC considered that an ICER of \$75,000 to < \$95,000/QALY or lower was reasonable for pembrolizumab plus lenvatinib in the all-comer population given the level of OS benefit observed in the KN775 trial, and the high clinical need in this patient population in which there have been no recent advances in therapy.
- 7.14 The PBAC noted that the financial estimates did not estimate the cost of combination therapy and pembrolizumab monotherapy separately, nor specifically separate out pMMR and dMMR patients. The main adjustment for the differing populations and regimens was an assumption regarding the proportion of patients eligible for lenvatinib, which the submission stated was based on the proportion of patients with pMMR in the KN775 trial (84.3% of patients in the trial were pMMR). The pre-PBAC response stated that it applied 75% as the ‘proportion of patients receiving lenvatinib (representing pMMR patients)’. The PBAC considered that the proportion of patients who initiate lenvatinib may be higher than 75%, and close to 100%, given its advice that the restriction should allow use of combination therapy in all-comers.
- 7.15 The PBAC considered the parameters for estimating the financial implications described in the pre-PBAC response were reasonable, with the following exceptions: (a) the proportion of patients treated first line should remain at 70% (rather than increase to 75% as proposed in the pre-PBAC response); (b) the proportion of patients with ECOG 0 or 1 should remain at 80% (rather than increase to 83% as proposed in the pre-PBAC response); (c) as outlined in Paragraph 7.14, the proportion of patients who initiate lenvatinib may be higher than 75%, and close to 100%.

- 7.16 The PBAC also considered that, in the financial estimates, the average number of doses per patient of pembrolizumab and lenvatinib should be consistent with those estimated in the economic model.
- 7.17 The PBAC advised that a RSA would be required to manage the financial risk of utilisation outside the intended population and the potential for use for longer durations than estimated. The PBAC advised that any rebates for expenditure above the caps should be high in order to adequately manage these risks.
- 7.18 The PBAC considered that the listings for pembrolizumab plus lenvatinib should:
- be 'Authority Required (streamlined)';
  - allow use of either pembrolizumab or lenvatinib as single agents if a patient develops an intolerance (as proposed by the sponsor);
  - allow use of pembrolizumab as a single agent in patients in whom lenvatinib is contraindicated; and
  - state 'Patient must have received a prior platinum-based chemotherapy regimen for this condition'.
- 7.19 The PBAC noted that the TGA had recently approved a pembrolizumab dosing regimen of 400 mg every six weeks (in addition to the 200 mg every three week regimen, which was assumed in the submission) across all indications, but that the sponsor had not specifically requested listing of this regimen in this indication. The PBAC advised that it would be appropriate for the pembrolizumab listing to also allow use of the 400 mg every six week regimen.

*Pembrolizumab monotherapy in the dMMR population*

- 7.20 The PBAC did not recommend the listing of pembrolizumab for use as monotherapy in patients with deficient DNA mismatch repair (dMMR) endometrial cancer. The PBAC considered that the clinical benefit of monotherapy, which was based on a relatively small single arm study, was uncertain. Further, the PBAC considered that the incremental benefit versus chemotherapy had not been adequately quantified in the submission, and thus the cost-effectiveness could not be assessed. As outlined above, the PBAC recommended that combination therapy with pembrolizumab and lenvatinib be available for all-comers (including patients with dMMR) consistent with the KN775 trial.
- 7.21 The PBAC noted that the clinical evidence to support the efficacy of pembrolizumab monotherapy was from a small single arm study, KN158. This was a 'basket study' of multiple cohorts of patients with various tumours, in which 90 patients had dMMR endometrial cancer. The submission presented a naïve side-by-side comparison of point estimates of OS observed in KN158 versus the chemotherapy arm of the dMMR subgroup in KN775. The PBAC considered there was a high risk of bias with this analysis given the naïve nature of the comparison. The PBAC considered that, although the claim of superior efficacy for pembrolizumab monotherapy in patients with dMMR

tumours was likely supported, the magnitude of any incremental benefit could not be determined based on the evidence provided.

- 7.22 The submission had also included a naïve side-by-side comparison of pembrolizumab monotherapy (from KN158) versus the pembrolizumab plus lenvatinib arm of the dMMR subgroup in KN775. The PBAC considered that this comparison was also subject to a high risk of bias, and the committee considered that (though not the relevant comparison at the time the submission was made) there was insufficient evidence to support a comparative assessment between pembrolizumab monotherapy and pembrolizumab plus lenvatinib combination therapy.
- 7.23 The PBAC noted that randomised trial data were available to support the use of combination therapy with pembrolizumab plus lenvatinib in this cohort of patients, albeit included in the ITT population of the KN775 trial.
- 7.24 The PBAC considered that the claim of superior comparative safety of pembrolizumab monotherapy versus chemotherapy was not adequately supported, noting that no comparative safety data was presented in the submission.
- 7.25 As outlined above, the submission did not specifically assess the cost-effectiveness of pembrolizumab monotherapy versus chemotherapy (instead only modelling combination therapy based on the ITT results from KN775). Further, the PBAC considered that the incremental benefit versus chemotherapy had not been adequately quantified in the submission, and thus the cost-effectiveness could not be assessed.

#### General

- 7.26 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically the PBAC found that in the circumstances of its recommendation for pembrolizumab in combination with lenvatinib:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over chemotherapy on the basis of the OS gain observed in KN775;
  - b) The treatment is expected to address a high and urgent unmet clinical need in the proposed population;
  - 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
- 7.27 The PBAC noted that this submission is not eligible for an Independent Review as a positive recommendation had been made.

#### **Outcome:**

Recommended

## 8 Recommended listing

Amend existing listing as follows:

Pembrolizumab (initial, continuing and grandfather):

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Amount	No. of Rpts	Available brands
PEMBROLIZUMAB				
pembrolizumab 100 mg/4 mL injections, 4 mL vial	New (public) New (private)	200 mg	6	Keytruda

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID  (for internal Dept. use)	<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction Type</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new]
	<b>Episodicity:</b> 3 weekly treatment
	<b>Severity:</b> advanced, metastatic or recurrent
	<b>Condition:</b> endometrial carcinoma
	<b>Indication:</b> Advanced, metastatic or recurrent endometrial carcinoma
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised
	Administrative Advice Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333
	<b>Treatment Phase:</b> Initial treatment
	<b>Clinical criteria:</b>
	Patient must have received a prior platinum-based chemotherapy regimen for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor or any prior tyrosine kinase inhibitor for this PBS indication
	<b>AND</b>
	<b>Clinical criteria:</b>
	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
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be in combination with PBS-subsidised lenvatinib for this condition, unless the patient has a contraindication to lenvatinib or an intolerance to lenvatinib requires a temporary or permanent discontinuation of lenvatinib
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not exceed a total of 7 doses under this restriction
	<b>Administrative Advice:</b> In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later

Public Summary Document – March 2022 PBAC Meeting with March 2023 Addendum

	<b>Treatment Phase:</b> Continuing treatment
	<b>Clinical criteria:</b>
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be in combination with PBS-subsidised lenvatinib for this condition, unless the patient has a contraindication to lenvatinib or an intolerance to lenvatinib requires a temporary or permanent discontinuation of lenvatinib
	<b>Clinical criteria:</b>
	The treatment must not exceed a total of 35 doses or up to 24 months of combined initial and continuing treatment in a lifetime for this condition whichever comes first

	<b>Treatment Phase:</b> Transitioning from non-PBS to PBS subsidised treatment – ‘Grandfather’ treatment
	<b>Clinical criteria:</b>
	Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have received a prior platinum-based chemotherapy regimen for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have received prior PBS funded treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor or any prior tyrosine kinase inhibitor for endometrial cancer
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have had a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of no higher than 1 prior to initiation of non-PBS-subsidised treatment with this drug and lenvatinib for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be in combination with PBS-subsidised lenvatinib for this condition, unless the patient has a contraindication to lenvatinib or an intolerance to lenvatinib requires a temporary or permanent discontinuation of lenvatinib
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not exceed a total of 35 doses or up to 24 months of combined initial and continuing treatment in a lifetime for this condition whichever comes first
	<b>Prescribing instruction:</b>
	A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria

Public Summary Document – March 2022 PBAC Meeting with March 2023 Addendum

Lenvatinib

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Quantity (packs)	Max. Amount (units)	No. of Rpts	Available brands
LENVATINIB					
lenvatinib capsules 4 mg, 30	New	2	60	2	Lenvima
lenvatinib capsules 10 mg, 30	New	2	60	2	

(for internal Dept. use)	<b>Concept ID</b>	<b>Category / Program:</b> General Schedule – Section 85
		<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
		<b>Restriction Type</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new]
		<b>Severity:</b> advanced, metastatic or recurrent
		<b>Condition:</b> endometrial carcinoma
		<b>Indication:</b> Advanced, metastatic or recurrent endometrial carcinoma
		<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
		<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised
		Administrative Advice Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333
		<b>Treatment Phase:</b> Initial treatment
		<b>Clinical criteria:</b>
		Patient must have received a prior platinum-based chemotherapy regimen for this condition

	<b>Treatment Phase:</b> Continuing treatment
	<b>Clinical criteria:</b>
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug

	for this condition.
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be in combination with PBS subsidised pembrolizumab for this indication, unless the patient (i) has completed the equivalent of 35 doses of 3 weekly regimen of pembrolizumab, or (ii) develops an intolerance to pembrolizumab and requires a temporary or permanent discontinuation of pembrolizumab

	<b>Treatment Phase:</b> Transitioning from non-PBS to PBS subsidised treatment – ‘Grandfather’ treatment
	<b>Clinical criteria:</b>
	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have received a prior platinum-based chemotherapy regimen for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have received prior PBS-subsidised treatment with a programmed cell death-1 (PD-1) inhibitor or programmed cell death ligand-1 (PD-L1) inhibitor or any tyrosine kinase inhibitor for this PBS indication
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have had a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of no higher than 1 prior to initiation of non-PBS-subsidised treatment with this drug and pembrolizumab for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be in combination with PBS subsidised pembrolizumab for this indication, unless the patient has completed 35 doses of pembrolizumab or develops an intolerance to pembrolizumab and requires a temporary or permanent discontinuation of pembrolizumab.
	<b>Prescribing instruction:</b>
	A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria

***These restrictions may be subject to further review, including to accommodate for the pembrolizumab 400 mg every six week regimen. Should there be any changes made to the restriction the Sponsor will be informed.***

## 9 Context for Decision

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

or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **10 Sponsor's Comment**

MSD welcomes the positive recommendation given the high unmet need for effective therapies to treat this condition. However, MSD is disappointed that the PBAC did not recommend the listing of pembrolizumab for use as monotherapy in those patients with deficient DNA mismatch repair (dMMR). The recommendation for the use of pembrolizumab in combination with lenvatinib in dMMR patients is outside of the approved TGA indication and therefore problematic for sponsors.

MSD will be looking to work closely with the Department of Health to work through the challenges resulting from this recommendation to ensure that this combination therapy is made available to Australian patients as soon as possible.

## Addendum to the March 2022 PBAC Public Summary Document:

### 11 Purpose

- 11.1 To provide the PBAC with an update on the status of listing negotiations between the Department and the respective sponsors for pembrolizumab and lenvatinib.
- 11.2 To seek the PBAC’s advice at its March 2023 meeting regarding whether the cost per patient based on the current price offers for pembrolizumab and lenvatinib for the treatment of endometrial cancer is acceptably cost-effective.

### 12 Background

- 12.1 At its March 2022 meeting, the PBAC recommended the listing of pembrolizumab+lenvatinib for the treatment of patients with advanced endometrial cancer who have disease progression following prior systemic therapy regardless of biomarker status.
- 12.2 Pembrolizumab and lenvatinib are marketed by different sponsors. Subsequent to the March 2022 recommendation, the sponsors of pembrolizumab and lenvatinib, Merck Sharp & Dohme (MSD) and Eisai respectively, submitted separate listing proposals for endometrial cancer to the Department. The Department has been engaging with each sponsor separately, █
- 12.3 Following negotiations, the sponsors have presented prices that result in a total patient cost of \$█, which is higher than the price calculated based on the PBAC advice in March 2022 (\$█).
- 12.4 The Department seeks PBAC advice as to whether the proposals from the sponsors are acceptable.

### 13 Details of the proposals

- 13.1 Based on the March 2022 advice, the cost per patient of pembrolizumab+lenvatinib was to be \$█. This cost is based on the assumptions that were used for the economic model.

Table 17: Drug cost per patient for pembrolizumab and lenvatinib in March 2022

Drug	Number of administrations			Total cost per course	
	KN775	Model	Financial	Model	Financials
<b>Pembrolizumab plus lenvatinib</b>					
Pembrolizumab	12.1	█ <sup>a</sup>	█ <sup>b</sup>	\$█	\$█
Lenvatinib	8.4 “months”	█ “months” at █% dose intensity <sup>c</sup>	█ months at dose of █ mg <sup>d</sup>		
Total					

Source: Table 14, Ratified PBAC minutes, item 6.07 pembrolizumab March 2022

- 13.2 A summary of the prices proposed by the sponsors, and resulting cost per patient, is shown below.

**Table 18: Drug cost per patient for pembrolizumab and lenvatinib at March 2023**

Drug	Unit price proposed	Cost per patient per course
Pembrolizumab	\$ [redacted] per 100 mg vial	\$ [redacted]
Lenvatinib	\$ [redacted] per 30 pack (10 mg and 4 mg)	\$ [redacted]
<b>Total</b>		<b>\$ [redacted]</b>

13.3 At a total cost of \$ [redacted] patient per course, the calculated ICER is \$75,000 to < \$95,000/QALY.

13.4 The table below presents the updated financial estimates of pembrolizumab+lenvatinib (at the proposed effective unit prices) to the PBS/RPBS for the treatment of endometrial cancer.

**Table 19: Indicative cost of listing pembrolizumab + lenvatinib**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Net cost PBS / RPBS (\$)</b>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>

The redacted values correspond to the following ranges:

<sup>1</sup> \$10 million to < \$20 million

13.5 In March 2022, the PBAC advised that a Risk Sharing Arrangement (RSA) would be required to manage the financial risk of utilisation outside the intended population and the potential for use for longer durations than estimated and that any rebates for expenditure above the caps should be high in order to adequately manage these risks. MSD in its pricing offer proposed a reimbursement of [redacted]% to manage the financial risk associated with any expenditure above the subsidisation caps. [redacted]

## 14 PBAC Outcome

14.1 The PBAC noted the sponsors' price offers for pembrolizumab and lenvatinib for the treatment of endometrial cancer, resulting in a total cost per patient per course of \$ [redacted] and a resulting ICER of \$75,000 to < \$95,000/QALY. The PBAC noted that its March 2022 recommendation was based on an ICER of \$75,000/QALY or lower.

14.2 The PBAC recalled that there was clear benefit observed in all-comers in the key trial (KN775) and further noted the high clinical need in this patient population in which there have been no recent advances in therapy. In the context of the updated financial estimates of a net cost to the PBS/RPBS of \$70 million to < \$80 million to \$80 million to < \$90 million over 6 years, the PBAC considered that, on balance, a resulting ICER of \$75,000 to < \$95,000/QALY was acceptably cost-effective.

14.3 The PBAC reiterated that a RSA would be required to manage the financial risk of utilisation outside the intended population and the potential for use for longer durations than estimated. The PBAC noted MSD's offer of [redacted]% rebate above caps in the updated pricing proposal. The PBAC advised that at least a [redacted]% rebate above caps would be required, consistent with its March 2022 advice around an appropriate RSA, and especially in the context of the higher revised ICER.

**Outcome:**

Advice provided

## **15 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.

## **16 Sponsor's Comment**

The sponsor had no comment.