An addendum to this public summary document has been included at the end of the document.

# 7.03 DOSTARLIMAB, Solution concentrate for I.V. infusion 500 mg in 10 mL, Jemperli®, GlaxoSmithKline Australia Pty Ltd.

## 1 Purpose of submission

1.1 The Standard Re-entry submission requested a Section 100 listing for dostarlimab for the treatment of recurrent or advanced (A/R) mismatch repair deficient (dMMR) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen. This was the second submission for dostarlimab. Dostarlimab is not currently PBS-listed.

1.2 Listing was requested on the basis of: (i) a cost-effectiveness analysis versus standard of care (SoC) comprising single agent chemotherapy and platinum-based chemotherapy (PBC); and (ii) a cost-minimisation approach versus pembrolizumab + lenvatinib (PEM+LEN). The resubmission stated that the final effective price for dostarlimab would be determined based on the economic evaluation the PBAC considers appropriate for decision-making, which was expected to depend on whether the sponsors of PEM+LEN have commenced the PBS listing process by the time of the November 2022 PBAC meeting.

1.3 Table 1 presents the key components of the clinical issue addressed by the resubmission.

**Table 1: Key components of the clinical issue addressed by the resubmission**

| Component | Description | |
|---|---|---|
| Population | Patients with recurrent or advanced (A/R) mismatch repair deficient (dMMR) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen. | |
| Intervention | Dostarlimab 500 mg Q3W given intravenously (IV) for the first four doses, followed by 1,000 mg Q6W for all cycles thereafter for up to 2 years. | |
| Comparator | Main comparator | Standard of care (SoC) comprising single-agent and platinum-based chemotherapies |
| | Near market comparator [a,b] | Pembrolizumab 200mg IV Q3W plus lenvatinib 20mg daily orally (PEM+LEN): clinical and economic comparator<br>Pembrolizumab 200mg IV Q3W monotherapy: supplementary clinical comparator |
| Outcomes | Objective response rate, duration of response, progression-free survival, overall survival, safety. | |
| Clinical claim | In patients with A/R dMMR EC that has progressed on or following prior treatment with a platinum-containing regimen:<br>Dostarlimab is superior in terms of efficacy and non-inferior in terms of safety compared with SoC.<br>[b] Dostarlimab is non-inferior in terms of efficacy and superior in terms of safety compared with PEM+LEN.<br>Dostarlimab is non-inferior in terms of efficacy and safety compared with pembrolizumab monotherapy. | |

Source: Table 3, p 23 of the resubmission.
A/R = recurrent or advanced; dMMR = mismatch repair deficient; EC = endometrial cancer; Q3W = every 3 weeks; Q6W = every 6 weeks; PEM+LEN = pembrolizumab plus lenvatinib; SoC = standard of care
[a] The near market comparators PEM+LEN and pembrolizumab monotherapy were not presented in the previous dostarlimab submission.
[b] The resubmission stated that of the two near market comparators, PEM+LEN was considered to be the more relevant as it was recommended for listing in A/R EC following PBC (irrespective of MMR status), whereas pembrolizumab monotherapy was not recommended for listing in A/R dMMR EC following PBC.
Underlined text indicates changes since the previous dostarlimab submission.

# 2 Background

## *Registration status*

2.1 Dostarlimab was registered, with provisional approval, on 17 February 2022 for the following indication: "JEMPERLI is indicated as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen."

2.2 The dostarlimab Product Information (PI) states: "This medicine and indication have provisional approval, based on objective response rate and duration of response in a single-arm trial. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials."

## *Previous PBAC consideration*

2.3 Dostarlimab for the treatment of A/R dMMR EC that has progressed on or following prior PBC was previously considered by PBAC in March 2022.

2.4 At the March 2022 PBAC meeting, PEM+LEN and pembrolizumab monotherapy (referred to as pembrolizumab ± lenvatinib from herein) were also considered for A/R EC that has progressed on or following prior PBC. PEM+LEN was recommended for the treatment of advanced, metastatic or recurrent EC in patients who have received a prior PBC regimen for this condition, irrespective of MMR status. Pembrolizumab

monotherapy was not recommended. At the time of PBAC consideration PEM+LEN had not been listed on the PBS for the treatment of EC.

2.5 Table 2 summarises the key matters from the previous PBAC consideration and how the resubmission addressed those concerns.

**Table 2: Summary of key matters of concern**

| Component | Matter of concern | How the resubmission addresses it |
|---|---|---|
| Requested restriction | The PBAC considered that the requested listing and restrictions were generally appropriate and should also specify that the patient has not received prior PD-(L)1 therapy for this condition (paragraph 7.2, dostarlimab PSD, March 2022 PBAC meeting). | Addressed. Restriction amended to reflect PBAC comments. |
| Comparator | Overall, the PBAC considered that the nominated comparator was appropriate, however noted that, should pembrolizumab ± lenvatinib be PBS listed in this indication, it may become the relevant comparator for dostarlimab (paragraph 7.4, dostarlimab PSD, March 2022 PBAC meeting). | Addressed. The resubmission nominated the following comparators:<br>Main comparator: SoC; comprising single-agent and platinum-based chemotherapies.<br>Near market comparator:<br>PEM+LEN: clinical and economic comparator<br>Pembrolizumab monotherapy: supplementary clinical comparator (see paragraph 5.1) |
| Clinical evaluation | The PBAC considered that a comparison with pembrolizumab ± lenvatinib, to support a claim of non-inferior effectiveness, would require full independent evaluation (paragraph 7.8, dostarlimab PSD, March 2022 PBAC meeting). | Addressed. Naïve indirect comparison with pembrolizumab ± lenvatinib presented. |
| Clinical effectiveness | The evidence submitted for dostarlimab was based on a relatively small single arm study with immature follow-up and considered there were key transitivity and methodological issues with the indirect comparisons presented in the submission.<br>The PBAC considered that the magnitude of benefit for dostarlimab over chemotherapy was uncertain (paragraph 7.1, dostarlimab PSD, March 2022 PBAC meeting). | The evaluation considered this was not adequately addressed. As in the previous dostarlimab submission, the evidence consisted of only one single arm study of dostarlimab, GARNET. The naïve indirect comparisons presented by the resubmission involved various arms of different trials which lead to a high risk of bias and the results of the analysis were highly uncertain. (paragraphs 6.12 to 6.23) |
| Clinical effectiveness | The PBAC noted that even with the longer follow-up (data cut IA3) for GARNET Cohort A1 provided in the PSCR, the OS data were relatively immature with median survival not reached (paragraph 7.5, dostarlimab PSD, March 2022 PBAC meeting). | The evaluation considered this was not adequately addressed. Data from GARNET Cohort A1 data cut IA3 were used in the clinical evaluation in the resubmission. (paragraphs 6.12 to 6.23) |
| Pending clinical data | The PBAC noted there was an on-going randomised, double-blind phase III study of dostarlimab + chemotherapy versus chemotherapy alone in patients with recurrent (first recurrence only) or primary advanced EC, the RUBY trial. The PBAC considered that evidence from the RUBY trial may shift the clinical place for dostarlimab to the first line setting in combination with chemotherapy (paragraph 7.3, dostarlimab PSD, March 2022 PBAC meeting). | Partially addressed. Results for the RUBY trial were not provided in the resubmission. The resubmission reported that the primary completion date for the RUBY trial is estimated to occur in 2022 (with exact timings based on PFS events). |

| Component | Matter of concern | How the resubmission addresses it |
|---|---|---|
| Safety | The PBAC considered that the safety comparison of dostarlimab to SoC was limited due to inconsistent reporting of disaggregated safety outcomes across the included studies and because relatively few patients have been exposed to the approved dostarlimab dose, with limited follow-up (paragraph 7.7, dostarlimab PSD, March 2022 PBAC meeting). | The evaluation considered this was not adequately addressed. Safety data for GARNET cohort A1 data cut IA3 was presented in the resubmission, which provided limited additional data compared to data presented in the previous submission. For PEM+LEN and pembrolizumab monotherapy, the resubmission stated that event specific safety data were inconsistently reported across the identified studies and no comparative safety data was provided. (paragraphs 6.28 to 6.32) |
| Comparison versus pembrolizumab ± lenvatinib | The PBAC considered that a comparison with pembrolizumab ± lenvatinib would require a full analysis as per the PBAC guidelines and evaluation (paragraph 7.12, dostarlimab PSD, March 2022 PBAC meeting). | Addressed. The resubmission presented a cost minimisation analysis of dostarlimab versus PEM+LEN in A/R dMMR EC following PBC. This was consistent with the clinical claims of non-inferior effectiveness and superior safety proposed for dostarlimab relative to PEM+LEN in Section 2 (paragraphs 6.48). No analysis against pembrolizumab monotherapy was conducted as it was not recommended for listing by PBAC. |
| Economic evaluation | The PBAC considered a resubmission for dostarlimab may require additional longer-term data to support the modelled OS benefit, however the PBAC noted that additional data is not expected until 2024. The PBAC considered that a conservative modelling approach would be required to address the uncertainty in the magnitude of benefit and long-term OS for dostarlimab (paragraph 7.12, dostarlimab PSD, March 2022 PBAC meeting). | Partially addressed. The IA3 GARNET data-cut (previously presented in the PSCR for the previous submission) was incorporated into the model, increasing the applied KM data from 12.5 months to 27.6 months in the dostarlimab arm of the model. The time horizon was reduced from 10 years to 6 years, with curve convergence applied between 4 and 6 years (paragraph 6.51). |
| Financial estimates | The PBAC considered that the submission's financial estimates appeared underestimated. (paragraph 7.11, dostarlimab PSD, March 2022 PBAC meeting). | Partially addressed. A number of PBAC and DUSC recommendations were incorporated into the financial estimates, but the evaluation considered the number of eligible patients in the resubmission may still be underestimated as prevalent patients were not included in the financial estimates (5.07.DUSC ADV.2, March 2022), stage III patients who would be treated with curative intent were not considered (5.07.DUSC ADV.5, March 2022) and the proportion of patients receiving 1L PBC after listing of dostarlimab was likely underestimated (See Table 23). These issues were subsequently addressed in the PSCR. |

Source: Table 1, p19 of the resubmission

A/R = recurrent or advanced; dMMR = mismatch repair deficient; DUSC = Drug Utilisation Sub Committee; EC = endometrial cancer; IA3 = interim analysis 3; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBC = platinum-based chemotherapy; PBS = Pharmaceutical Benefits Scheme; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death-ligand protein 1; PEM+LEN = pembrolizumab plus lenvatinib; PSCR = pre-subcommittee response; PSD = Public Summary Document; SoC = standard of care.

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

# 3 Requested listing

3.1 The restriction requested in the resubmission is outlined below. Secretariat suggested additions are in italics and deletions are in strikethrough.

| **MEDICINAL PRODUCT medicinal product pack** | **Dispensed Price for Max. Amount** | **Max. amount (units)** | **№.of Rpts** | **Available brands** |
|---|---|---|---|---|
| Initial treatment | | | | |
| Dostarlimab 500mg/10mL injection, 1 x 10mL vial | $[redacted] (public, published)<br>$[redacted] (private, published)<br>$[redacted] (public, effective)<br>$[redacted] (private, effective) | 500 mg | 3 | Jemperli |

| | |
|---|---|
| Category/Program: | Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals |
| Prescriber type: | Medical Practitioners |
| Restriction type: | ☒ ~~Streamlined~~<br>☒ *Authority Required (telephone/online PBS authorities system)* |
| Severity: | Recurrent or advanced |
| Condition: | ~~Mismatch repair deficient~~ endometrial cancer |
| Indication: | Recurrent or advanced ~~mismatch repair deficient (dMMR)~~ endometrial cancer |
| Treatment Phase: | Initial |
| Clinical criteria: | Initial<br>Patient must have received a prior platinum-based chemotherapy regimen for this condition,<br>AND<br>Patient must have a~~n ECOG~~ *WHO* performance status of 0 or 1,<br>AND<br>~~Patient must have~~ *The condition must be* mismatch repair deficient (dMMR) ~~endometrial~~ *type* cancer, as determined by immunohistochemistry test,<br>AND<br>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~~ *this condition* |
| Administrative Advice: | *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333*<br>~~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.~~<br>*No increase in the maximum quantity or number of units may be authorised*<br>No increase in the maximum number of repeats may be authorised.<br>Special Pricing Arrangements apply. |

| Continuing treatment | | | | |
|---|---|---|---|---|
| Dostarlimab 500mg/10mL injection, 1 x 10mL vial | $[redacted] (public, published)<br>$[redacted] (private, published)<br>$[redacted] (public, effective)<br>$[redacted] (private, effective) | 1,000 mg | 3 | Jemperli |

| | |
|---|---|
| Treatment Phase: | Continuing |
| Clinical criteria: | Patient must have previously received PBS-subsidised treatment with this drug for this condition,<br>AND<br>Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition,<br>AND<br>The treatment must not exceed a maximum total of 24 months in a lifetime for this condition. |
| Administrative advice: | *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333*<br>*No increase in the maximum quantity or number of units may be authorised* |

| | |
|---|---|
| | No increase in the maximum number of repeats may be authorised.<br>Special Pricing Arrangements apply. |
| | |
| Treatment Phase: | Transitioning from non-PBS to PBS subsided treatment – 'Grandfather' treatment |
| Clinical criteria: | Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date],<br>AND<br>Patient must have received a prior platinum-based chemotherapy regimen for this condition,<br>AND<br>Patient must *have had a WHO* performance status of 0 or 1 prior to initiation of non-PBS-subsidised treatment with this drug for this condition,<br>AND<br>~~Patient must have~~ *The condition must be* mismatch repair deficient (dMMR) ~~endometrial~~ *type* cancer, as determined by immunohistochemistry test,<br>AND<br>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~~ *this condition*,<br>AND<br>Patient must not have developed disease progression while receiving *non*-PBS-subsidised treatment with this drug for this condition,<br>AND<br>The treatment must not exceed a maximum total of 24 months in a lifetime for this condition. |
| Prescribing Instructions: | 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. |
| Administrative Advice: | *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333*<br>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.<br>~~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.~~<br>*No increase in the maximum quantity or number of units may be authorised*<br>No increase in the maximum number of repeats may be authorised.<br>Special Pricing Arrangements apply. |

3.2 The effective price requested in the resubmission was [redacted]% lower (per 500 mg vial) than in the previous submission (dispensed prices were $[redacted] (public) and $[redacted] (private) in previous submission). The requested approved ex-manufacturer price (AEMP) of $[redacted] was [redacted]% lower than in the pre-PBAC response for the previous submission ($[redacted]). The pre-PBAC response further reduced the proposed price to $[redacted] AEMP per 500 mg vial. The sponsor stated this was to address any remaining uncertainty associated with reliance on single-arm study data.

3.3 In the previous submission, the PBAC considered that the requested listing and restrictions were generally appropriate and should also specify that the patient has not received prior PD-(L)1 therapy for this condition (paragraph 7.2, dostarlimab Public Summary Document [PSD], March 2022 PBAC meeting). The resubmission incorporated all wording changes suggested by the Secretariat (paragraph 3.1, dostarlimab PSD, March 2022 PBAC meeting).

3.4 Unlike the provisional TGA indication, the requested restriction did not specify that:

- dostarlimab must be used as monotherapy; or
- the patient's disease must have progressed on or following treatment with a platinum-containing regimen, simply that patients must have received a prior platinum-based chemotherapy regimen for this condition.

While the latter was consistent with the PBAC's advice for pembrolizumab + lenvatinib restriction (paragraph 3.4, pembrolizumab PSD, March 2022 PBAC Meeting), the ESC noted that the proposed restriction was broader than the TGA indication and considered that this may lead to use in a patient population whose disease has not progressed on or following treatment with a platinum-containing regimen, and these patients were not represented in the GARNET trial.

3.5 The requested restriction specified a maximum treatment duration of 24 months, which was consistent with the recommended listing for pembrolizumab (in combination with lenvatinib) for the treatment of EC. In GARNET Cohort A1, patients were treated for up to two years but treatment could continue beyond two years if the treating physician and the sponsor agreed that the patient would continue to benefit from the treatment.

3.6 The Secretariat noted that the restriction could be simplified by combining the initial, continuing and grandfather treatment phases into a single treatment phase.

3.7 The resubmission stated that a patient access program for dostarlimab was anticipated to commence in [redacted] with eligibility to be aligned with the proposed PBS restriction. A grandfather listing was requested, and the resubmission estimated that < 500 patients would move from the access program to PBS-subsidised treatment.

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

# 4 Population and disease

4.1 EC is the most common type of cancer of the uterus and accounts for about 95% of all cases of uterine cancer, the most common gynaecological cancer diagnosed in Australian women (AIHW, 2021; Cancer Council, 2021). Despite currently available treatment, an estimated 13% of patients with EC will experience disease recurrence (Fung-Kee-Fung, 2006), while a recent study by Francis (2019) of 2,691 women with early stage (stage I/II) EC diagnosed from 2000 to 2016, reported an overall recurrence rate of 7.2% (194/2691), with a median follow-up of 6.1 years.

4.2 Endometrial cancers may be classified based on the mismatch repair (MMR) status, as normal (proficient) mismatch repair (pMMR) or dMMR tumours. EC is associated with dMMR in up to 33% of cases (Morona, 2020; Scarpa, 2016). dMMR tumours can develop microsatellite instability (MSI), which is a change in the length of repetitive sequences in tumour DNA compared with normal DNA. Therefore, MSI-H is the observable characteristic (phenotype) displayed when errors occur in the DNA MMR

system (Luchini, 2019). The resubmission claimed that dMMR status is predictive of clinical benefit from PD-1 inhibitors that block PD-1's interaction with its ligands, restoring cytotoxic T-cell activity and freeing the T-cell to kill the tumour cell (Le, 2017; Zhao, 2019).

# 5 Comparator

5.1 The previous submission nominated SoC comprising single-agent chemotherapy and PBC as the main comparator, which was considered appropriate by the PBAC (paragraph 7.4, dostarlimab PSD, March 2022 PBAC meeting). In addition to SoC, the resubmission nominated PEM+LEN and pembrolizumab monotherapy as near market comparators. Overall, the nominated comparators were appropriate. The ESC considered that, for patients with dMMR status, the option of dostarlimab (a single agent therapy) may be useful given that guidelines recommend a single agent to reduce potential toxicity. The PBAC recalled that it had recommended that the restriction for PEM+LEN should allow use of single agent pembrolizumab in patients who experience toxicity with lenvatinib or in whom lenvatinib is contraindicated.

*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 noted that, for patients with metastatic endometrial cancer, chemotherapy is generally associated with poor long-term disease control and low quality of life and there is a high unmet need for access to effective treatments outside the clinical trial setting. The clinician considered that immunotherapy is the preferred treatment option for patients with dMMR endometrial cancer. The clinician noted that there is evidence across several immunotherapies that patients experience a prolonged benefit that substantially improves survival. The clinician noted that oncologists are familiar with managing the toxicities associated with immunotherapy and that chemotherapies are more challenging to administer due to patient comorbidities and prior therapies. The clinician stated that some oncologists would prefer to use a single agent immunotherapy (rather than in combination with lenvatinib) due to significant rates of hypertension and other toxicities when using lenvatinib treatment in combination with immunotherapy.

## *Consumer comments*

6.2 The PBAC noted and welcomed the input from one health care professional and two organisations via the Consumer Comments facility on the PBS website. Input from the health professional outlined that metastatic endometrial cancer is a devastating diagnosis with few effective second line treatments. The comments also noted that dostarlimab is well-tolerated and effective.

6.3 Comments from Rare Cancers Australia noted that patients with endometrial cancer can experience a loss of dignity associated with invasive treatments and medical procedures. Comments also reported that published evidence suggests that between 20% and 30% of endometrial cancers are associated with dMMR or high microsatellite instability (MSI-H), characteristics that render the tumour more sensitive to immune checkpoint inhibitors. Comments also noted that there is a high unmet need for effective and tolerable treatment options in endometrial cancer.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the dostarlimab submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the GARNET study. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for dostarlimab, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[1], based on a comparison with chemotherapy.

## *Clinical studies and trials*

6.5 No relevant head-to-head trials comparing dostarlimab for the treatment of A/R dMMR EC following PBC versus SoC, PEM+LEN or pembrolizumab monotherapy were identified in the resubmission.

6.6 The resubmission was based on:

- Naïve indirect comparisons of dostarlimab with SoC[2] constructed using the single arm GARNET study and the individual comparator arms of four different trials (ZoptEC, IXAMPLE2, KEYNOTE-775 (chemotherapy arm) and Scambia 2020). An inverse probability of treatment weighting (IPTW) analysis was also presented using available individual patient data (IPD) comparing dostarlimab (informed by the GARNET study (Cohort A1) study, which included only patients with dMMR status) to doxorubicin (informed by the SoC arm of the ZoptEC trial). In addition, a retrospective cohort study in the UK RWE was used to inform the SoC arm in sensitivity analyses of the economic model. These trials and studies were the same as those presented in the previous submission.
- Naïve indirect comparisons of dostarlimab versus PEM+LEN or pembrolizumab monotherapy[3] constructed using the GARNET study and individual comparator

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

[2] *Note that the results presented in relation to the indirect comparison are derived from ad-hoc/ post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for GARNET (Cohort A1) and comparator trials. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

[3] *Note that the results presented in relation to the indirect comparison are derived from ad-hoc/ post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for GARNET (Cohort A1) and comparator trials. Interpretation of the results and their*

arms of KEYNOTE-775 (PEM+LEN arm) and KEYNOTE-158 (pembrolizumab monotherapy arm). This data was not presented in the previous submission. However, it was presented in the previous Pre-Sub-Committee Response (PSCR) and the PBAC has previously considered the results of KEYNOTE-775 and KEYNOTE-158 in the consideration of pembrolizumab ± lenvatinib in A/R EC at its March 2022 meeting.

6.7 A summary of the included trials and studies and the relevant arms used to inform the current submission is presented in Table 3 below.

**Table 3**: **Summary of identified trials and studies**

| Study/trial | Intervention (n) | Comparator (n) |
|---|---|---|
| **Dostarlimab** | | |
| GARNET | Dostarlimab (Cohort A1, data cut IA3 n=153) | NA |
| **SoC** | | |
| ZoptEC | Zoptarelin doxorubicin (n=256) | Doxorubicin (n=255) |
| IXAMPLE2 | Ixabepilone (n=248) | Paclitaxel or doxorubicin (n=248) |
| KEYNOTE-775 | Pembrolizumab + lenvatinib (ITT n=411) | Paclitaxel or doxorubicin (n=416) |
| Scambia 2020 | Sapanisertib + paclitaxel (n=90)<br>Sapanisertib (n=41)<br>Sapanisertib + serabelisib (n=20) | Paclitaxel (n=90) |
| UK RWE | NA | Single agent and combination platinum and non platinum chemotherapy. (n=999) |
| **Pembrolizumab +/- lenvatinib** [a] | | |
| KEYNOTE-775 | Pembrolizumab + lenvatinib (ITT n=411; dMMR N=65) | Paclitaxel or doxorubicin (n=416) |
| KEYNOTE-158 | Pembrolizumab (MSI-H/ dMMR N=90) | NA |

Source: constructed during evaluation.
ITT = intention to treat; dMMR = mismatch repair deficient; MSI-H = high microsatellite instability; n = number of participants; NA = not applicable; SoC = standard of care.
a KEYNOTE-775 and KEYNOTE-158 were considered by the PBAC in the submission for pembrolizumab for the treatment of patients with advanced endometrial cancer who have disease progression following prior systemic therapy at the March 2022 PBAC meeting
Shaded cells indicate evidence used to support resubmission.
Underlined text indicates new data for the dostarlimab resubmission.

6.8 Details of the trials and studies presented in the resubmission are provided in Table 4.

**Table 4: Overview of trials, studies and associated reports presented in the submission**

| Study identifier (ID) | Reports | Content |
|---|---|---|
| GARNET | A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an Anti-PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors - Part 2B, Endometrial Cancer (Cohorts A1 and A2) [IA2 data-cut] | Clinical Study Report dated 16 November 2020 |
| | A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an Anti-PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors - Part 2B, Endometrial Cancer (Cohorts A1 and A2) [IA3 data-cut] | Clinical Study Report dated 6 May 2022 |
| | Oaknin A, Tinker AV, Gilbert L, Samouëlian V, Mathews C, Brown J, et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients with Recurrent or Advanced Mismatch | JAMA Oncology. 2020;6(11):1766-72. |

*application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

| Study identifier (ID) | Reports | Content |
|---|---|---|
| | Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. | |
| | Oaknin A, Gilbert L, Tinker AV, Brown J, Mathews C, Press J, et al. Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: Interim results from GARNET - A phase I, single-arm study. | Journal for ImmunoTherapy of Cancer. 2022;10(1). |
| ZoptEC | Aeterna Zentaris. STUDY CODE: AEZS-108-050. Randomized controlled study comparing AEZS 108 with doxorubicin as second line therapy for locally advanced, recurrent or metastatic endometrial cancer. Report of Statistical Results – Tables and Graphs | Individual patient data 09 May 2017. |
| | Miller DS, Gabra H, Emons G, McMeekin DS, Oza AM, Temkin SM, et al. ZoptEC: Phase III study of zoptarelin doxorubicin (AEZS-108) in platinum-taxane pretreated endometrial cancer (Study AEZS-108-050). | Journal of Clinical Oncology 2014;32(15). |
| IXAMPLE2 | McMeekin S, Dizon D, Barter J, Scambia G, Manzyuk L, Lisyanskaya A, et al. Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer. | Gynecologic Oncology 2015;138(1):18-23. |
| KEYNOTE-775 | Makker V, Colombo N, Herráez AC, 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. Society of Gynecologic Oncology. Virtual Annual Meeting on Women's Cancer 2021. [a] | Conference presentation |
| | Makker V, Colombo N, Herráez AC, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. | New England Journal of Medicine. 2022;386(5):437-48. |
| Scambia 2020 (NCT02725268) | Scambia G, Han SN, Oza AM, Colombo N, Oaknin A, Raspagliesi F, et al. Randomized phase II study of sapanisertib (SAP) + paclitaxel (PAC) versus PAC alone in patients (pts) with advanced, recurrent, or persistent endometrial cancer. | Conference abstract Journal of Clinical Oncology 2020; 38, (15 SUPPL). |
| KEYNOTE-158 [b] | Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, de Jesus-Acosta A, Delord JP, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/ mismatch repair–deficient cancer: Results from the phase II KEYNOTE-158 study. | Journal of Clinical Oncology. 2020;38(1):1-10. |
| | O'Malley DM, Bariani GM, Cassier PA, Marabelle A, Hansen AR, De Jesus Acosta A, et al. Pembrolizumab in Patients With Microsatellite Instability–High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study. | Journal of Clinical Oncology. 2022;40(7):752-61. |

Source: Table 20, p61-65 of the resubmission.
a KEYNOTE-755 data for this publication (abstract) were previously seen by the PBAC (pembrolizumab + lenvatinib submission).
b KEYNOTE-158 data were previously seen by the PBAC (pembrolizumab + lenvatinib submission) from the publication O'Malley et al. Blue shading indicates trials included in the previous dostarlimab submission.
Pembrolizumab in Patients with Microsatellite Instability-High (MSI-H) Advanced Endometrial Cancer: Updated results from KEYNOTE 158. ESMO 2021 virtual meeting presentation. This publication was not referenced in the resubmission.

6.9 GARNET is a single-arm, open-label, first-in-human phase I/II study of dostarlimab in patients with advanced solid tumours. The previous resubmission presented GARNET data from data cut IA2 (median follow up 12.5 months), whereas the resubmission (and the previous PSCR) provided data from IA3 (median follow up 27.6 months). The most relevant patient cohort investigated by GARNET was Cohort A1 (IA3, n=153; IA2, n=129) which enrolled dMMR/MSI-H EC patients who have progressed on or after

platinum doublet therapy. Cohort A2 enrolled pMMR/microsatellite stable (MSS) EC patients and therefore results are not included in this document. Other cohorts involved patients with other types of solid tumours and were therefore not included in the resubmission.

6.10 The key features of the included evidence are summarised in Table 5.

**Table 5: Key features of the included evidence – naïve indirect comparisons [a]**

| Trial | N | Design/ median duration of follow up | Risk of bias | Patient population | Outcome(s) | Use in modelled evaluation |
|---|---|---|---|---|---|---|
| **Dostarlimab** | | | | | | |
| GARNET Cohort A1 | 153 | SA, OL/ Cohort A1 data cut IA3 ITT 27.6 months | High | A/R dMMR EC following PBC | OS, PFS, ORR | Survival gain |
| **SoC [b]** | | | | | | |
| ZoptEC | 249 | OL, R/ 26.7 months | High [b] | Locally advanced, recurrent, or metastatic EC, following PBC | OS, PFS, ORR | Survival gain for SoC |
| IXAMPLE2 | 248 | OL, R/ NR | High [b] | Locally advanced, recurrent, or metastatic EC, following PBC | OS, PFS, ORR | Used in sensitivity analysis |
| KEYNOTE-775 (chemotherapy arm) | 416 | OL, R/ 10.7 months | High [b] | Advanced, recurrent or metastatic EC, following PBC | OS, PFS, ORR | Used in sensitivity analysis |
| Scambia 2020 | 90 | OL, R / 14.4 months | High [b] | Advanced, recurrent, or persistent EC, following PBC | OS, PFS, ORR | Not used |
| UK RWE study | 45,494 | Descriptive, non-interventional/ GARNET-like loose cohort: 27.4 months; GARNET-like strict cohort: 27.0 months [c] | High [d] | Patients diagnosed with between 01/01/2013 and 31/12/2018 in England. | OS, TTNT, TTD | Used in sensitivity analysis |
| **PEM+LEN** | | | | | | |
| KEYNOTE-775 (PEM+LEN arm) | 411 | OL, R 12.2 months | High [b] | Advanced, recurrent or metastatic EC, following PBC | OS, PFS, ORR | Survival gain |
| **Pembrolizumab monotherapy** | | | | | | |
| KEYNOTE-158 | 79 | SA, OL 42.6 months | High | Advanced (unresectable and/or metastatic) MSI-H/dMMR EC, following "standard therapies" | OS, PFS, ORR | Survival gain |

Source: Tables 21, 22, pp 70, 72 of the resubmission.

A/R = advanced or recurrent; dMMR = mismatch repair deficient; EC = endometrial cancer; NR = not reported; OL = open label; ORR = objective response rate; OS = overall survival; PBC = platinum-based chemotherapy; PFS = progression-free survival; R = randomised, SA = single arm, TTD = time to treatment discontinuation; TTNT = time to next treatment.

a For the included trials, only the arms for which the resubmission presented information for have been included.

b Even though ZoptEC, IXAMPLE2, KEYNOTE-775 and Scambia 2020 were randomised trials, only the single treatment arms of interest were included in the clinical evaluation by the resubmission. Therefore, the risk of bias from using data from only the comparators in these trials should be considered high as the benefits of randomisation for the respective trials were not retained.

c From the UK RWE, a "GARNET-like cohort", matched to GARNET Cohort A1 was created post hoc. Two sub-cohorts, referred to as the "GARNET-like (loose) cohort" (included patients with baseline PS ≤1 or missing data) and the "GARNET-like (strict) cohort" (included only patients with baseline PS ≤1), were used in the naïve comparison to dostarlimab by the submission.

d Only selected results were provided from the UK RWE for evaluation, which may be a source of reporting bias. Moreover, the UK RWE did not meet the criteria for inclusion in the systematic review but was included by the submission on an ad hoc basis, which may increase the risk of selection bias.

6.11 None of the trials informing the SoC arm restricted patient enrolment by MMR status. However, as in the previous submission, the resubmission considered that MMR status was not a treatment effect modifier for chemotherapy in A/R EC and claimed that the inclusion of all-comers in the SoC trials compared to dMMR patients in

GARNET Cohort A1 was not expected to limit the exchangeability of the trials. The ESC had previously considered there was a lack of evidence regarding whether or not MMR status was a treatment effect modifier for chemotherapy but considered the fact that the comparator studies included all-comers (rather than being restricted to dMMR patients) may have biased against dostarlimab (paragraph 6.11, dostarlimab PSD, March 2022).

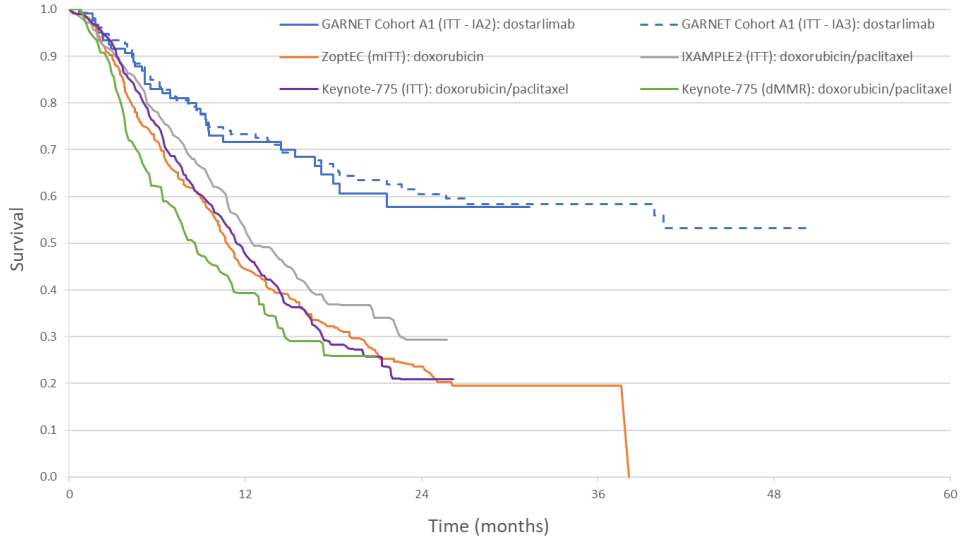
## *Comparative effectiveness*

Efficacy outcomes presented by the submission

6.12 As in the previous submission, the naïve indirect comparisons involved comparing various arms of different trials conducted at different time periods in different patient populations. Therefore, there was a high risk of bias and the results of this analysis were highly uncertain.

6.13 For the comparison of dostarlimab and SoC, the OS Kaplan-Meier curves of the relevant arms of the included trials and studies and key OS outcomes are presented in Figure 1 and Table 6.

**Figure 1: Dostarlimab vs SoC naïve comparison: Kaplan-Meier overall survival curves from included trials***




Source: Figure 32, p156 of the resubmission.
dMMR = mismatch repair deficient; ITT = intention-to-treat; mITT = modified intention-to-treat.
Note: OS curves were generated via the digitising of KM curves reported in: GARNET IA2 CSR; GARNET IA3 CSR; ZoptEC IPD (data on file); McMeekin 2015; Makker 2022; Makker 2021 (IGCS). The anonymised ZoptEC IPD has been licensed to GSK from Aeterna Zentaris GmbH for indirect comparison purposes (unpublished data).
**Note that the Kaplan-Meier plots depicted in Figure 1 are presented specifically for the purposes of informing the PBAC consideration. Their interpretation and application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

**Table 6: Dostarlimab vs SoC naïve comparison: Summary of OS events in the relevant arms of included trials and studies**

| Trial | Analysis set | N | Deaths, n (%) | Censored, n (%) | Median, months (95%CI) | 12-month survival % | 24-month survival % |
|---|---|---|---|---|---|---|---|
| **Dostarlimab (Interim Analysis 3)** | | | | | | | |
| GARNET Cohort A1 | ITT [b] | 153 | 57 (37.3) | 96 (62.7) | NR (27.1, NR) | 73.3 | 60.5 [c] |
| | PES [b] | 143 | 55 (38.5) | 88 (61.5) | NR (25.7, NR) | 71.4 | 59.8 [c] |
| | MAS* | 128.2 | 44.6 (34.8) | 83.6 (65.2) | NR (39.9, NR) | N/R [d] | N/R [d] |
| **SoC** | | | | | | | |
| ZoptEC (doxorubicin) [a] | mITT | 249 | 188 (75.5) | 61 (24.5) | 10.8 (9.8, 12.6) | 44.6 [c] | 23.5 [c] |
| | MAS# | 237 | 177 (74.8) | 60 (24.9) | 11.2 (10.2, 13.4) | N/R [d] | N/R [d] |
| IXAMPLE2 (paclitaxel or doxorubicin) | ITT | 248 | 98 (39.5) | 150 (60.5) | 12.3 (10.7, 15.4) | 53.7 [c] | 29.3 [c] |
| KEYNOTE-775 (paclitaxel or doxorubicin) | ITT | 416 | 245 (58.9) | 171 (41.1) | 11.4 (10.5, 12.9) | 47.9 [e] | 21.4 [e] |
| | dMMR | 65 | 42 (64.6) | 23 (35.4) | 8.6 (5.5, 12.9) | 39.4 [c] | 25.8 [c] |
| Scambia 2020 (paclitaxel) | ITT [c] | 90 | 58 (64) | 32 (36) | 12.7 (9.8, 19.6) | N/R [d] | N/R [d] |

Sources: Table 43, p115 and Table 70, p166 of the resubmission, Table 16, p57, Table 14.2.22a and Table 14.2.23a of the GARNET Clinical Study Report.

CI = confidence interval; dMMR = mismatch repair deficient; FU = follow- up; ITT = intention-to-treat; MAS= adjusted matched analysis set, mITT = modified intention-to-treat; pMMR = mismatch repair proficient, NR = not reached; N/R = not reported; PES = Primary Efficacy Set.

a The anonymised ZoptEC IPD was licensed to GSK from Aeterna Zentaris GmbH for indirect comparison purposes (unpublished data).

b For GARNET, the primary efficacy set included patients with measurable disease at baseline (assessed based on RECIST v1.1 by blinded independent central review (BICR)), who had the opportunity for at least 24 weeks of tumour assessment at the time of analysis. Of the 153 patients in the ITT cohort in GARNET Cohort A1 (IA3), a total of 10 patients did not have measurable lesions by BICR at baseline, resulting in a primary efficacy set of 143 (93.5%) patients.

c These data are not reported and were estimated via the digitisation of published KM curves.

d These data are not reported, and KM data is not available for landmark survival estimates.

e These figures were not able to be independently verified in the commentary.

Blue shading indicates data previously seen by the PBAC.

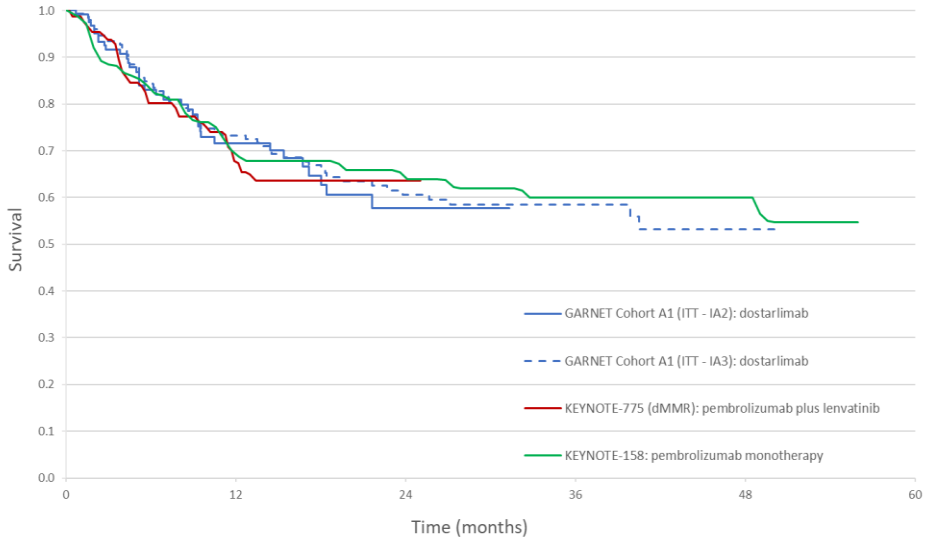
* *Note that the MAS results are derived from a post-hoc analysis performed specifically for the purposes of informing the PBAC consideration. This analysis was not part of the pre-specified statistical plan for GARNET. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

\# *Note that the MAS results are derived from a post-hoc analysis performed specifically for the purposes of informing the PBAC consideration. This analysis was not part of the pre-specified statistical plan for ZoptEC. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.14 Median OS was not reached in GARNET Cohort A1 after a median follow up of 27.6 months. The resubmission noted that the updated OS lower confidence limit for GARNET Cohort A1 IA3 data cut (ITT: 27.1 months) had increased since the IA2 data cut (ITT: 18.4 months) with plateauing of survival observed from the prior data-cut maintained out to four years. However, the plateauing may be related to a decreasing number of patients at risk at later time points (e.g. only five patients remain at risk at 48 months).

6.15 For the comparison of dostarlimab and PEM+LEN or pembrolizumab monotherapy, the OS Kaplan-Meier curves of the relevant arms of the included trials and studies and key OS outcomes are presented in Figure 2 and Table 7.

**Figure 2: Dostarlimab vs pembrolizumab +/- lenvatinib naïve comparison: Kaplan-Meier OS curves from included trials***




Source: Figure 34, p161 of the resubmission.
dMMR = mismatch repair deficient; ITT = intention-to-treat.
Note: OS curves were generated via the digitising of KM curves reported in: GARNET IA2 & IA3 CSR; Makker 2022; O'Malley 2022.
* *Note that the Kaplan-Meier plots depicted in Figure 2 are presented specifically for the purposes of informing the PBAC consideration. Their interpretation and application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

**Table 7: Dostarlimab vs pembrolizumab +/- lenvatinib naïve comparison: Summary of OS events in the relevant arms of included trials and studies**

| Trial | Analysis set | N | Deaths, n (%) | Censored, n (%) | Median, months (95%CI) | 12-month survival % | 24-month survival % |
|---|---|---|---|---|---|---|---|
| **Dostarlimab** | | | | | | | |
| GARNET Cohort A1 | ITT | 153 | 57 (37.3) | 96 (62.7) | NR (27.1, NR) | 73.3 | 60.5 [a] |
| | PES | 143 | 55 (38.5) | 88 (61.5) | NR (25.7, NR) | 71.4 | 59.8 [a] |
| **Pembrolizumab + Lenvatinib** | | | | | | | |
| KEYNOTE-775 | ITT | 411 | 188 (45.7) | 223 (54.3) | 18.3 (15.2, 20.5) | 62.5 | 42 |
| | dMMR | 65 | 23 (35.4) | 42 (64.6) | NR (NR,NR) | 67.9 [a] | 63.6 [a] |
| **Pembrolizumab monotherapy** | | | | | | | |
| KEYNOTE-158 | dMMR (EAP) | 79 | 29 (36.7) | 50 (63.3) | NR (27.2, NR) | 69 | 64 |

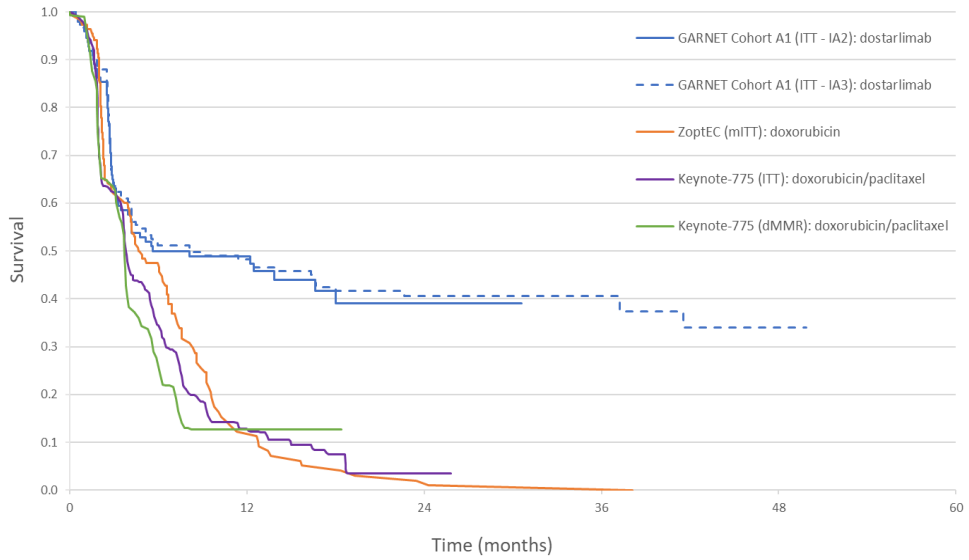
Sources: Table 44, p116 of the resubmission, Table 16, p57, Table 14.2.22a and Table 14.2.23a of the Clinical Study Report.
CI = confidence interval; dMMR = mismatch repair deficient; EAP = efficacy analysis population; ITT = intention-to-treat; N/R = not reached; NR= not reached; PES = Primary Efficacy Set
a These data are not explicitly reported, therefore were estimated via the digitisation of published KM curves.
Blue shading indicates data previously seen by the PBAC (pembrolizumab + lenvatinib or dostarlimab submission).

6.16 As for GARNET Cohort A1, results from the dMMR population in KEYNOTE-775 and KEYNOTE-158 have yet to reach median OS. While GARNET Cohort A1 and the pembrolizumab arm of KEYNOTE-158 had similar lower 95% confidence limit values, the immaturity of the data sets in the dMMR population and the lack of formal statistical testing limits the ability to draw meaningful conclusions regarding the comparative OS efficacy between dostarlimab and pembrolizumab ± lenvatinib in dMMR patients. Nonetheless based on the visual inspection of the Kaplan-Meier OS

curves, the available evidence appears to suggest that OS in dMMR patients treated with dostarlimab and pembrolizumab ± lenvatinib were similar.

6.17 The PFS Kaplan-Meier curves and key PFS outcomes of the relevant arms of the included trials and studies comparing dostarlimab and SoC are presented in Figure 3 and Table 8.

**Figure 3: Dostarlimab vs SoC naïve comparison: Kaplan-Meier progression-free survival curves from included trials [a,*]**




Source: Figure 33, p157 of the resubmission.
dMMR = mismatch repair deficient; ITT = intention-to-treat; mITT = modified intention-to-treat.
a Not all of the identified trials provided Kaplan-Meier curves for PFS.
Note: PFS curves were generated via the digitising of KM curves reported in: GARNET IA2 CSR; GARNET IA3 CSR; ZoptEC IPD (data on file); Makker 2022; Makker 2021 (IGCS). The anonymised ZoptEC IPD has been licensed to GSK from Aeterna Zentaris GmbH for indirect comparison purposes (unpublished data).
* *Note that the Kaplan-Meier plots depicted in Figure 3 are presented specifically for the purposes of informing the PBAC consideration. Their interpretation and application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

**Table 8: Dostarlimab vs SoC naïve comparison: Summary of PFS events in the relevant arms of included trials and studies**

| Trial | Analysis set | N | Events, n (%) | Censored, n (%) | Median, months (95%CI) | 12-month PFS % | 24-month PFS % |
|---|---|---|---|---|---|---|---|
| **Dostarlimab** | | | | | | | |
| GARNET Cohort A1 | ITT | 153 | 87 (56.9) | 66 (43.1) | 8.3 (4.2, 18.0) | 48.2 | 40.6 [c] |
| | PES | 143 | 83 (58.0) | 60 (42.0) | 6.0 (4.1, 18.0) | 46.4 | 40.0 [c] |
| | MAS* | 128.2 | 70.9 (55.3) | 57.3 (44.7) | 12.2 (4.21, 41.6) | N/R | N/R |
| **SoC** | | | | | | | |
| ZoptEC (doxorubicin) [a] | mITT | 249 | 148 (59.4) | 101 (40.6) | 4.7 (4.1, 6.6) | 12.3 [b] | 2.1 [b] |
| | MAS# | 237 | 138 (58.2) | 99 (41.8) | 6.05 (4.17, 6.70 | N/R | N/R |
| IXAMPLE2 (paclitaxel or doxorubicin) | ITT | 223 | 162 (72.6) | 61 (27.4) | 4.0 (2.7, 4.3) | N/R [c] | N/R [c] |
| KEYNOTE-775 (paclitaxel or doxorubicin) | ITT | 416 | 286 (68.8) | 130 (31.3) | 3.8 (3.6, 4.2) | 13.2 | 3.8 |
| | dMMR | 65 | 48 (73.8) | 17 (26.2) | 3.7 (3.1, 4.4) | 12.7 [b] | N/R |
| Scambia 2020 (paclitaxel) | ITT [b] | 90 | N/R | N/R | 3.7 (2.3, 4.5) | N/R [c] | N/R [c] |

Sources: Table 47, p125 of the resubmission, Table 14.2.10a of the GARNET CSR, Table 18 and 19, p35 ZoptEC report -final report (GARNET IA3)_ZoptEC analysis

CI = confidence interval; dMMR = mismatch repair deficient; ITT = intention-to-treat; MAS= adjusted matched analysis set; mITT = modified intention-to-treat; N/R = not reported; PES = Primary Efficacy Set, PFS = progression free survival; pMMR = mismatch repair proficient.

a The anonymised ZoptEC IPD has been licensed to GSK from Aeterna Zentaris GmbH for indirect comparison purposes (unpublished data).

b These data are not reported, therefore are estimated via the digitisation of published KM curves.

c These data are not reported, and KM data is not available for landmark survival estimates.

Blue shading indicates data previously seen by the PBAC.

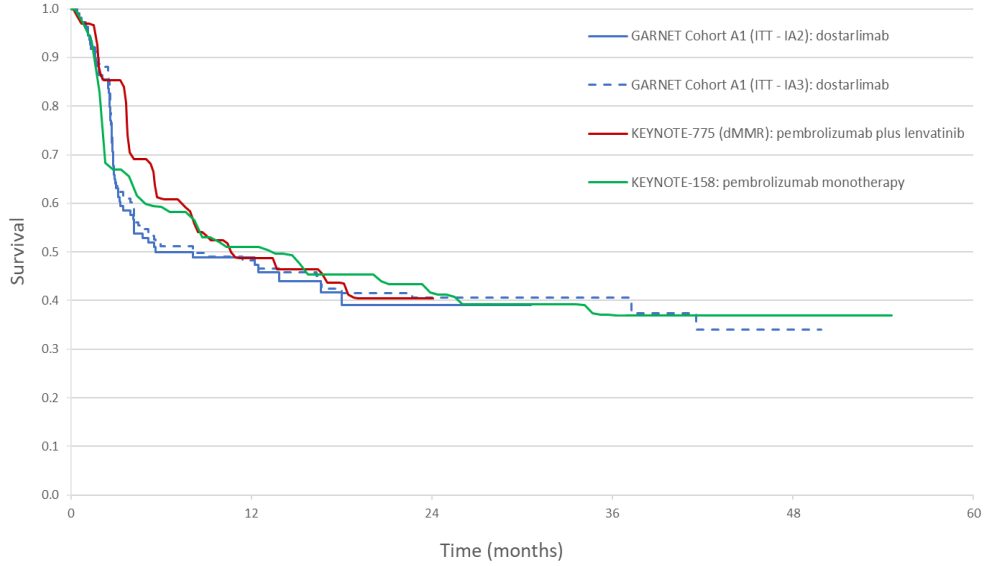
* *Note that the MAS results are derived from a post-hoc analysis performed specifically for the purposes of informing the PBAC consideration. This analysis was not part of the pre-specified statistical plan for GARNET. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

# *Note that the MAS results are derived from a post-hoc analysis performed specifically for the purposes of informing the PBAC consideration. This analysis was not part of the pre-specified statistical plan for ZoptEC. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.18 While the resubmission proposed an MCID for PFS of 2.5 months, it was unclear if it was appropriate to apply an MCID to a naïve indirect comparison given the high risk of bias of using individual arms from different studies. Given the lower 95% CI of all dostarlimab arms (irrespective of cohort, analysis set or data cut) was lower than 9.1 months (6.6 months, the highest 95% confidence interval PFS value reported for SoC in ZoptEC plus 2.5 months), the nominated MCID for PFS was not met.

6.19 Kaplan-Meier curves showing an overlay of PFS results for the dostarlimab versus pembrolizumab ± lenvatinib included trials and studies are provided in Figure 4. The comparison of PFS is presented in Table 9.

**Figure 4: Dostarlimab vs pembrolizumab +/- lenvatinib naïve comparison: Kaplan-Meier PFS curves from included trials***




Source: Figure 35, p161 of the resubmission.
dMMR = mismatch repair deficient; ITT = intention-to-treat.
Note: PFS curves were generated via the digitising of KM curves reported in: GARNET IA2 & IA3 CSR; Makker 2022; O'Malley 2022.
* *Note that the Kaplan-Meier plots depicted in Figure 4 are presented specifically for the purposes of informing the PBAC consideration. Their interpretation and application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

**Table 9: Dostarlimab vs pembrolizumab +/- lenvatinib naïve comparison: Summary of PFS events in the relevant arms of included trials and studies**

| Trial | Analysis set | N | Events, n (%) | Censored, n (%) | Median, months (95%CI) | 12-month PFS % | 24-month PFS % |
|---|---|---|---|---|---|---|---|
| **Dostarlimab** | | | | | | | |
| GARNET Cohort A1 | ITT | 153 | 87 (56.9) | 66 (43.1) | 8.3 (4.2, 18.0) | 48.2 | 40.6 |
| | PES | 143 | 83 (58.0) | 60 (42.0) | 6.0 (4.1, 18.0) | 46.4 | 40.0 |
| **Pembrolizumab + Lenvatinib** | | | | | | | |
| KEYNOTE-775 | ITT | 411 | 281 (68.4) | 130 (31.6) | 7.2 (5.7, 7.6) | 31.2 | 20.9 |
| | dMMR | 65 | 34 (52.3) | 31 (47.7) | 10.7 (5.6, NR) | 48.7 [a] | 40.5 [a] |
| **Pembrolizumab monotherapy** | | | | | | | |
| KEYNOTE-158 | dMMR (EAP) | 79 | 45 (57.0) | 34 (43.0) | 13.1 (4.3, 34.4) | 51 | 41 |

Source: Table 48, p126 of the resubmission.
CI = confidence interval; dMMR = mismatch repair deficient; EAP = Efficacy Analysis Population; ES = Efficacy Set; FU = follow- up; ITT = intention-to-treat; NR = not reached; PES = Primary Efficacy Set; PFS = progression free survival; pMMR = mismatch repair proficient.
a These data are not explicitly reported, therefore are estimated via the digitisation of published KM curves.
Blue shading indicates data previously seen by the PBAC (pembrolizumab + lenvatinib submission).

6.20 In dMMR patients, the point estimates for median PFS were higher for those treated with pembrolizumab ± lenvatinib than those treated with dostarlimab in GARNET Cohort A1 (ITT: 8.3 months [95%CI 4.2, 18.0]), however due to the wide confidence intervals it was unclear if the results were significantly different. Visual inspection of the Kaplan-Meier curves also suggested that PFS over time was similar across all three treatment arms in the selected trials/studies, with the curves plateauing at around 35-40% for all three curves. As for OS, the plateauing may be related to having very few

patients at risk at later time points (GARNET Cohort A1, IA3: 2 patients at 48 months; KEYNOTE-775 (dMMR cohort): 1 patient at 24 months; KEYNOTE-158: 5 patients at 48 months).

6.21 ORR was also reported as a key outcome in the resubmission. An ORR of 45.5% (95% CI: 37.1, 54.0) was reported for dostarlimab in the primary efficacy set of GARNET Cohort A1. The resubmission considered that the differences in response rates favoured dostarlimab compared to SoC because the lower confidence limit for ORR with dostarlimab (37.1%) was higher than the upper confidence limit with SoC across the included studies (18.4%-26.5%). The evaluation considered that it was unclear whether these results were clinically meaningful, and an MCID for ORR was not nominated by the resubmission.

6.22 The resubmission reported that the ORRs were similar for dostarlimab in GARNET Cohort A1 (45.5%) compared to PEM+LEN in the dMMR cohort of KEYNOTE-775 (40%) and pembrolizumab monotherapy in KEYNOTE-158 (48%). There was a large degree of overlap between the 95% confidence intervals of the treatment arms investigated.

6.23 Patient reported outcomes including the EQ-5D-5L were listed as exploratory objectives for GARNET. The results of the EQ-5D-5L from GARNET were not provided in the resubmission and could not be extracted during the evaluation. The resubmission however, utilised the EQ-5D-5L results collected in GARNET A1 in the economic model.

IPTW adjusted indirect comparison[4]

6.24 The resubmission presented an updated IPTW adjusted indirect comparison of the dostarlimab arm of GARNET Cohort A1 (updated to use the IA3 data-cut, rather than the IA2 data-cut used in the previous submission's IPTW analysis) versus the doxorubicin arm of the ZoptEC trial using IPD. The analysis adjusted for differences in the timepoints for tumour assessments between the GARNET and ZoptEC studies and only included patients from ZoptEC who would be eligible for GARNET. The PBAC previously considered there were several limitations associated with the IPTW analysis (paragraph 6.29, dostarlimab PSD, PBAC meeting March 2022). Despite these weaknesses, the resubmission followed similar methodology, largely with the same limitations as in the previous submission. In particular: the two studies were conducted over different time periods; there was potential for unmeasured confounding; and patients were not matched for dMMR status (biomarker testing was not performed in ZoptEC).

6.25 The updated IPTW analysis reported a statistically significant improvement in OS for dostarlimab versus doxorubicin (HR = 0.294; 95% CI: 0.212, 0.406). The difference

[4] *Note that the IPTW adjusted analyses are derived from a post-hoc analysis performed specifically for the purposes of informing the PBAC consideration. This analysis was not part of the pre-specified statistical plan for GARNET and ZoptEC. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose*

between the IPTW analysis from the previous submission (HR = 0.41; 95% CI 0.28, 0.61) highlights the uncertainty with using immature data sets and the limitations of the IPTW described above.

## *Comparative harms*

6.26 A summary of safety outcomes reported across the included dostarlimab and SoC arms of the included trials and studies is presented in Table 10.

**Table 10: Summary of safety from included dostarlimab and SoC studies**

| Intervention | Dostarlimab | | Doxorubicin | Paclitaxel or doxorubicin | | | Paclitaxel |
|---|---|---|---|---|---|---|---|
| Trial ID | GARNET Cohort A1 | | ZoptEC [a] | IXAMPLE2 | KEYNOTE-775 | | Scambia 2020 [b] |
| Analysis set | Safety (IA2) | Safety (IA3) | Safety | Safety | Safety | dMMR safety | Safety |
| Median FU, months | 12.5 | 27.6 | 26.7 | NR | 10.7 | 12.0 | 14.4 |
| N | 129 | 153 | 249 | 239 | 388 | 63 | 87 |
| Any AEs, % | 95.3 | 99.3 | NR | 95.4 | 99.5 | 98.4 | 97.7 |
| Grade ≥3 AEs, % | 48.1 | 56.9 | 78.3 | NR | 72.7 | 73.0 | 54 |
| Serious AEs, % | 34.1 | 37.9 | 30.1 | 29.3 | 30.4 | 38.1 | 26.4 |
| AE resulting in treatment discontinuation, % | 11.6 | 15.7 | 15.3 | 15.5 | 8.0 | 6.3 | NR |
| TRAEs, % | 63.6 | 70.6 | NR | 90.0 | 93.8 | 88.9 | NR |
| Grade ≥3 TRAEs, % | 13.2 | 17.6 | NR | NR | 59.0 | 57.1 | NR |
| Serious TRAEs, % | 9.3 | 11.8 | NR | 12.0 | 14.2 | 17.5 | NR |
| TRAEs resulting in treatment discontinuation, % | 3.9 | 8.5 | NR | NR | 5.7 | 3.2 | NR |
| TRAEs resulting in death, % | 0 | 0 | NR | NR | 2.1 | 3.2 | NR |

Source: Table 50, p133 of the resubmission, Table 17 of the GARNET CSR.

AE = adverse event; FU = follow- up; ITT = intention-to-treat; NR = not reported; TEAE = treatment-emergent adverse event; TRAE = treatment related adverse event.

a The anonymised ZoptEC IPD has been licensed to GSK from Aeterna Zentaris GmbH for indirect comparison purposes (unpublished data).

b Treatment-related AEs are not available from Scambia (2020).

Note: Relative risk values were not presented for dostarlimab due to the number and variability of the trials and studies presented as comparators and in particular the lack of exchangeability arising from the use of single arms from different studies and trials (i.e. each treatment arm was effectively from a different single arm study).

Blue shading indicates trials included in the previous dostarlimab submission.

6.27 While noting limitations of the available safety data, the PBAC previously considered that the claim of non-inferior comparative safety may be reasonable and that safety outcomes are likely to be different for dostarlimab compared with chemotherapy, consistent with other PD-(L)1 inhibitors (paragraph 7.7, dostarlimab PSD, March 2022 PBAC meeting).

6.28 The ESC noted that there was an increase in the proportion of patients with AEs and TRAEs with the increased exposure to dostarlimab between IA2 and IA3. The ESC considered that the incidence of AEs for dostarlimab may continue to increase with more mature trial data.

6.29 A summary of safety outcomes reported across the included dostarlimab and pembrolizumab +/- lenvatinib trials and studies is presented in Table 11.

**Table 11: Summary of safety from included dostarlimab and pembrolizumab +/- lenvatinib studies**

| Intervention | Dostarlimab | | PEM+LEN | | Pembrolizumab |
|---|---|---|---|---|---|
| Trial ID | GARNET Cohort A1 | | KEYNOTE-775 | | KEYNOTE-158 [a] |
| Analysis set | Safety (IA2) | Safety (IA3) | Safety | dMMR | Safety |
| Median FU, months | 12.5 | 27.6 | 12.2 | 12.0 | 42.6 |
| N | 129 | 153 | 406 | 64 | 90 |
| Any AEs, % | 95.3 | 99.3 | 99.8 | 100.0 | NR |
| Grade ≥3 AEs, % | 48.1 | 56.9 | 88.9 | 95.3 | NR |
| Serious AEs, % | 34.1 | 37.9 | 52.7 | 68.8 | NR |
| AEs resulting in treatment discontinuation, % | 11.6 | 15.7 | 33.0 | 43.8 | NR |
| TRAEs, % | 63.6 | 70.6 | 97.3 | 96.9 | 75.6 |
| Grade ≥3 TRAEs, % | 13.2 | 17.6 | 77.8 | 85.9 | 12.2 |
| Serious TRAEs, % | 9.3 | 11.8 | 33.3 | 45.3 | NR |
| TRAEs resulting in treatment discontinuation, % | 3.9 | 8.5 | 26.6 | 32.8 | 6.7 |
| TRAEs resulting in death, % | 0 | 0 | 1.5 | 3.1 | 0 |

Source: Table 51, p134 of the resubmission, Table 17 of the GARNET CSR.

AE = adverse event; FU = follow- up; ITT = intention-to-treat; NR = not reported; TEAE = treatment-emergent adverse event; TRAE = treatment related adverse event.

a Only treatment-related AEs are available for KEYNOTE-158 (O'Malley 2022).

Blue shading indicates trials included in the previous dostarlimab submission.

Grey shading indicates data previously seen by the PBAC (pembrolizumab + lenvatinib submission).

6.30 The resubmission stated that event specific safety data were inconsistently reported across the identified studies and did not provide any comparative safety information to support the claim that dostarlimab is superior in terms of safety compared with PEM+LEN and non-inferior in terms of safety compared with pembrolizumab monotherapy. Table 12 provides a summary of the commonly reported TRAEs for dostarlimab in GARNET Cohort A1, PEM+LEN in KEYNOTE-775 and pembrolizumab monotherapy in KEYNOTE-158. Given the inconsistent reporting using single arms across different trials, the evaluation considered that any claims or conclusions of comparative safety based on the available data should be interpreted with caution.

**Table 12: Common TRAEs reported for dostarlimab (GARNET Cohort A1 IA3 data set), KEYNOTE-775 (ITT, PEM+LEN) and KEYNOTE-158 (pembrolizumab)**

| Trial ID | Dostarlimab GARNET Cohort A1 IA3 data-cut | PEM+LEN KEYNOTE-775 (ITT) [b] | Pembrolizumab KEYNOTE-158 |
|---|---|---|---|
| Median Follow up, months | 27.6 | 12.2 | 42.6 |
| N | 153 | 406 | 90 |
| **Any grade TRAE, n (%) [a]** | **108 (70.6)** | **395 (97.3)** | **NR (75.6)** |
| Diarrhoea | 25 (16.3) | 171 (42.1) | 14 (15.6) |
| Asthenia | 24 (15.7) | 75 (18.5) | NR |
| Fatigue | 21 (13.7) | 113 (27.8) | 19 (21.1) |
| Nausea | 19 (12.4) | 158 (38.9) | 13 (14.4) |
| Arthralgia | 16 (10.5) | 84 (20.7) | 13 (14.4) |
| Pruritus | 19 (12.4) | NR | 22 (24.4) |
| Anaemia | 11 (7.2) | 58 (14.3) | NR |
| Hypothyroidism | 17 (11.1) | 221 (54.4) | 12 (13.3) |
| Rash | 14 (9.2) | 47 (11.6) | 10 (11.1) |

Sources: Tables 52, 53 and 54, pp135, 136 and 137 of the resubmission, O'Malley 2022.
ITT = intention to treat; NR = not reported; PEM+LEN = pembrolizumab + lenvatinib; TRAE = treatment-related adverse event.
a Table presents TRAEs reported in over 20% of patients for any of the relevant treatment arms of GARNET Cohort A1 (IA3), KEYNOTE-775 or KEYNOTE-158.
b For PEM+LEN, individual any grade TRAEs could not be independently verified. The number of patients experiencing each TRAE was not provided in the resubmission. These figures were estimated by multiplying 406 x % of the TRAE.

6.31 Adverse events which were likely related to lenvatinib such as hypertension (248/406, 61.1%), decreased appetite (149/406, 36.7%) and proteinuria (102/406, 25.1%) were also reported in KEYNOTE-775 but the incidence of these events in GARNET was low (hypertension: 1/153 (0.7%), decreased appetite: 8/153 (5.2%), proteinuria: 1/153 (0.7%)).

6.32 As noted previously, the number of patient-years of treatment with dostarlimab was low (paragraph 6.38, dostarlimab PSD, March 2022 PBAC meeting) and therefore the long-term safety with dostarlimab was uncertain. Nonetheless, the PBAC had previously considered that the safety of dostarlimab may be consistent with other PD-(L)1 inhibitors (paragraphs 6.34 and 7.7, dostarlimab PSD, March 2022 PBAC meeting). The ESC noted the limitations of the safety data available, however, overall, considered that dostarlimab alone appears less toxic than the combination of PEM+LEN.

## *Benefits/harms*

6.33 A summary of the comparative survival benefits for dostarlimab versus SoC (doxorubicin) based on the IPTW analysis (adjusted) is presented in the Table 13.

**Table 13: Summary of OS with adjusting stabilised-IPTW***

| **Benefits** | | | |
|---|---|---|---|
| **Analysis** | **Dostarlimab Events, n/N (%)** | **Doxorubicin Events, n/N (%)** | **HR (95% CI)** |
| **Overall survival** | | | |
| IPTW adjusted analysis | GARNET Cohort A1 (adjusted MAS): 44.6/128.2 (34.8) | ZoptEC (adjusted MAS): 177/237 (74.8) | **0.294 (0.212, 0.406)** |

Source: Tables 70 and 71, p167 of the resubmission

CI = confidence interval; HR = hazard ratio; IPTW = inverse probability treatment weighting; MAS = main analysis set (for adjusted indirect comparison); n = number of participants with event; N = total participants in group.

**Note that the IPTW adjusted analyses are derived from a post-hoc analysis performed specifically for the purposes of informing the PBAC consideration. This analysis was not part of the pre-specified statistical plan for GARNET and ZoptEC. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose*

6.34 On the basis of the IPTW analysis (adjusted) informed by the indirect naïve evidence presented by the resubmission, the comparison of dostarlimab and doxorubicin resulted in:

- Approximately a 70.6% reduction in death over a median duration of exposure of 11.2 months for doxorubicin.

However, the ESC considered the magnitude of the incremental benefit was highly uncertain given the key transitivity and methodological issues identified with the IPTW analysis (refer to Paragraph 6.40).

6.35 A comparison of harms is not presented for the comparison of dostarlimab versus SoC as the resubmission made a claim of non-inferiority.

6.36 While the resubmission made a claim of non-inferior efficacy and superior safety, the naïve indirect comparison presented in the resubmission did not allow for a quantitative comparison of the benefits and harms of dostarlimab and PEM+LEN. Accordingly, a benefits/harms table has not been presented.

6.37 As the resubmission made a claim of non-inferior efficacy and safety for dostarlimab versus pembrolizumab monotherapy, a benefits/harms table has not been presented.

## *Clinical claim*

Dostarlimab versus SoC:

6.38 As in the previous submission, the resubmission described dostarlimab as superior in terms of effectiveness and non-inferior in terms of safety compared to SoC in A/R dMMR EC following PBC.

6.39 The PBAC previously considered that "even with the longer follow-up provided in the PSCR (i.e. IA3), the OS data from GARNET Cohort A1 were relatively immature with median survival not reached" and that "the immaturity of the single-arm data from GARNET Cohort A1, along with the key transitivity and methodological issues identified with the IPTW analysis, limited the ability to assess the magnitude of any OS benefit from the indirect comparisons presented" (paragraph 7.5, dostarlimab PSD, March 2022 PBAC meeting).

6.40 The ESC considered that while it was reasonable to conclude that dostarlimab was superior in efficacy compared to SoC, the magnitude of the incremental benefit remains highly uncertain. The difference in OS appeared highly favourable towards dostarlimab, with the IPTW analysis estimating a hazard ratio for OS of 0.29 (95% CI: 0.21, 0.41); however, the ESC considered this analysis was unreliable due to key transitivity and methodological issues. Further, the OS benefit, which was estimated based on data from single arms of different studies, was greater than that observed in the randomised controlled trial of PEM+LEN versus SoC, KEYNOTE-775 (OS HR: 0.62 (95% CI: 0.51, 0.75) for the ITT population and 0.37 (95% CI: 0.22, 0.62) in the exploratory analysis of the dMMR subgroup). The ESC considered this further indicated that the IPTW and naïve indirect analyses had likely overestimated the treatment effect of dostarlimab versus SoC.

6.41 For the previous dostarlimab submission the PBAC considered that the safety comparison of dostarlimab to SoC was limited but considered that the claim of non-inferior comparative safety may be reasonable and that safety outcomes are likely to be different for dostarlimab compared with chemotherapy, consistent with other PD-(L)1 inhibitors (paragraph 7.7, dostarlimab PSD, March 2022 PBAC meeting). The ESC considered that while AEs reported in patients treated with dostarlimab in GARNET had increased for the IA3 data cut compared to IA2, the conclusion of non-inferior comparative safety remained reasonable.

6.42 The PBAC considered that the claim of superior comparative effectiveness versus SoC was reasonable, but the magnitude of the incremental benefit versus SoC was unable to be reliably estimated.

6.43 The PBAC considered that the claim of non-inferior comparative safety versus SoC was reasonable.

<u>Dostarlimab versus pembrolizumab ± lenvatinib:</u>

6.44 The resubmission described dostarlimab as non-inferior in terms of effectiveness and superior in terms of safety compared with PEM+LEN. The resubmission also described dostarlimab as non-inferior in terms of effectiveness and safety compared with pembrolizumab monotherapy.

6.45 The efficacy of dostarlimab appeared to be generally comparable to that of PEM+LEN however, the ESC considered that the clinical claim was uncertain due to the nature of the naïve indirect comparison of arms from different studies which was associated with high risk of bias and also due to the immaturity of the OS trial data.

6.46 The PBAC considered that the claim of non-inferior comparative effectiveness versus PEM+LEN was not adequately supported by the data.

6.47 The PBAC considered that the claim of superior comparative safety versus PEM+LEN was likely to be reasonable as combination use with lenvatinib is likely to add toxicity compared with single therapy.

## *Economic analysis*

6.48 The resubmission presented:

- a revised cost utility analysis (CUA) that incorporated data for the updated IA3 data-cut of GARNET Cohort A1 and applied modelling assumptions that were considered more conservative by the resubmission; and
- a cost-minimisation approach (CMA) versus PEM+LEN using published prices, based on the clinical claim of non-inferior effectiveness and superior safety for dostarlimab compared to PEM+LEN.

6.49 The resubmission stated that an economic evaluation of dostarlimab versus pembrolizumab monotherapy was not formally conducted due to the absence of a positive PBAC recommendation and a cost-effective price in this setting.

Dostarlimab versus SoC: CUA

6.50 As in the previous dostarlimab submission, the resubmission presented a stepped economic evaluation of dostarlimab versus SoC in A/R dMMR EC following PBC. The model was informed by data from the naïve indirect approach, with the dostarlimab arm of the model informed by the GARNET Cohort A1 study, and the SoC arm of the model informed by the doxorubicin arm of ZoptEC in the base case.

6.51 The structure and inputs of the updated model were predominantly the same as in the previous submission with the following key changes:

- The updated IA3 data-cut from GARNET Cohort A1 was incorporated into the model, increasing the period of applied KM data from 12.5 months to 27.6 months for the dostarlimab arm (in line with the median IA3 data-cut follow-up);
- The time horizon was reduced from 10 years to 6 years; and
- Convergence of the dostarlimab OS curve was applied between 4 and 6 years.

6.52 A summary of the economic model is presented in Table 14.

**Table 14: Summary of model structure, key inputs and rationale**

| Component | Description | Justification/comments |
|---|---|---|
| Interventions compared | Dostarlimab compared with doxorubicin | As for the previous dostarlimab model, the SoC arm in the base case was based on the doxorubicin arm of the ZoptEC trial. This was inconsistent with Section 2 of the resubmission where paclitaxel and doxorubicin were both presented as comparators. Use of alternative studies was presented as sensitivity analyses. |
| Type of analysis | Cost utility analysis | Consistent with the resubmission's clinical claim of superior effectiveness and non-inferior safety for dostarlimab compared to SoC. The PBAC previously found that "it was likely reasonable to conclude that dostarlimab has superior efficacy compared with SoC, (however) an adequate assessment of the magnitude of the OS benefit was not possible with the available data…" (paragraph 6.41, dostarlimab PSD, March 2022 PBAC meeting). |
| Outcomes | Life-years gained; Quality adjusted life years gained | Appropriate. |
| Time horizon | 6 years (vs median follow-up of 27.6 months in GARNET Cohort A1 IA3 data-cut) | "ESC considered that a shorter time horizon of 5 years may be more appropriate given the immature OS data from GARNET." (paragraph 6.56, dostarlimab PSD, March 2022 PBAC meeting). |
| Discount rate | 5% per annum | Reasonable |
| Method(s) used to generate results | Partitioned survival analysis | Reasonable |
| Health states | Progression-free; Progressed disease; Dead | Appropriate |
| Cycle length | 21 days | Reasonable |
| Allocation to health states | Dostarlimab arm: PFS and OS from GARNET Cohort A1 IA3 data-cut, followed by extrapolation of PFS and OS from 27.6 months<br>SoC arm: PFS and OS from ZoptEC, followed by extrapolation of PFS and OS from 26.7 months | Reasonable. Different parametric extrapolations were fitted in the sensitivity analysis of the resubmission. |
| Software | Microsoft Excel | Appropriate |

Source: Table 85, p195 of the resubmission.
OS = overall survival; PFS = progression-free survival; SoC = standard of care.

6.53 An outline of how the survival curves were constructed within the model base case is provided in Table 15.

**Table 15: Outline of survival curves applied in the model base case**

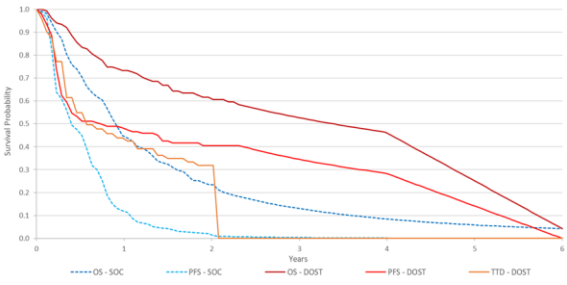
| Treatment arm | | Dostarlimab | SoC |
|---|---|---|---|
| Data source | | GARNET Cohort A1 IA3 data-cut | ZoptEC |
| PFS | Trial period | KM data<br>(Baseline to 27.6 months) | KM data<br>(Baseline to 26.7 months [a]) |
| | Extrapolation | Lognormal extrapolation (incorporating lifetables adjustment) from 27.6 to 48 months, followed by convergence to SoC PFS from 48 to 72 months | Lognormal extrapolation (incorporating lifetables adjustment) from 26.7 to 72 months |
| OS | Trial period | KM data<br>(Baseline to 27.6 months) | KM data<br>(Baseline to 26.7 months [a]) |
| | Extrapolation | Lognormal extrapolation (incorporating lifetables adjustment) from 27.6 to 48 months, followed by convergence to SoC OS from 48 to 72 months | Lognormal extrapolation (incorporating lifetables adjustment) from 26.7 to 72 months |
| TTD | Trial period | KM data<br>(Baseline to 24 months [b]) | Not applicable<br>(SoC treatment durations are applied directly at model entry) |
| | Extrapolation | Not required | |

Source: Table 99, p226 of the resubmission.
KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; SoC = standard of care; TTD = time to treatment discontinuation.
a Estimated median follow-up in the doxorubicin arm of ZoptEC, based on the reverse KM estimator method using the available survival IPD.
b In line with the maximum dostarlimab treatment duration applied in the model.

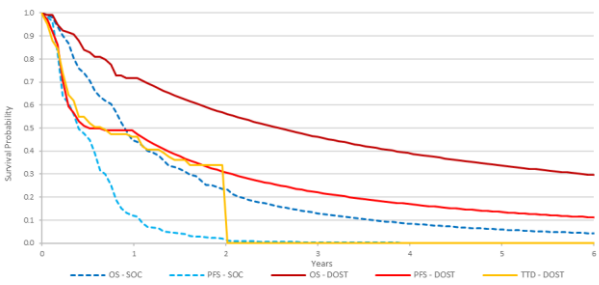
6.54 Survival curves applied in the model base case are illustrated in Figure 5. For comparison, the survival curves from the economic model in the previous submission base case are also provided, but over a six-year time horizon (rather than the 10-year time horizon used in the previous model).

**Figure 5: Comparison of survival curves applied in the model base case: resubmission and previous submission***

Parametrically extrapolated and converged survival curves applied in the model base case of the resubmission




Parametrically extrapolated and converged survival curves applied in the previous submission (March 2022) model base case




DOST = dostarlimab; PFS = progression-free survival; OS = overall survival; SOC = standard of care; TTD = time to treatment discontinuation
Sources: Figure 63, p226 of the resubmission. Constructed during evaluation using Jemperli (dostarlimab) 2L dMMR CUA_March 2022.xls. Based on the model provided in the previous submission, noting revised models were provided in the previous PSCR and pre-PBAC response.
**Note that the Kaplan-Meier plots and survival curves depicted in Figure 5 are presented specifically for the purposes of informing the PBAC consideration. Their interpretation and application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose*

6.55 The application of the convergence from year 4 to year 6 in the resubmission was clearly observable in Figure 5. However, prior to year 4, the resubmission's estimates of survival in the dostarlimab arm were more optimistic than in the previous

submission. For example, at three years, the resubmission estimated that 52.7% of patients in the dostarlimab arm remain alive, compared to 46.1% in the previous submission.

6.56 The OS extrapolation had a much larger impact on the economic analysis than the PFS extrapolation. However, due to the shorter time horizon in the current model as well as the forced convergence from year 4, the impact of the choice of parametric extrapolation was reduced (up to 6.8% change in ICER) compared to the previous submission (up to 42.6% change in ICER).

6.57 Table 16 summarises the key drivers of the economic model.

**Table 16: Key drivers of the model**

| Description | Method/Value | Impact<br>Base case: $[1] /QALY gained |
|---|---|---|
| Dostarlimab OS data | Based on data from the single-arm GARNET study (Cohort A1) in the dostarlimab arm and the doxorubicin arm of the ZoptEC trial in the SoC arm. The resulting difference in OS appeared highly favourable towards dostarlimab, and the ESC considered the magnitude of the incremental benefit was highly uncertain and likely overestimated. | Unable to be adequately tested in sensitivity analyses, but likely to be a key driver as indicated by the large incremental difference observed in Figure 1 and Figure 5. While the resubmission presented multivariate sensitivity analyses using alternative SoC studies, the ESC considered that the variation observed did not reflect the extent of uncertainty with regard to the clinical benefit. |
| Time horizon | The revised model base case presented in the resubmission applied a 6-year time horizon, reduced from the 10 years applied in the previous dostarlimab submission and 7.5 years applied in the PSCR of the previous submission. | Moderate, favoured dostarlimab. Changing the time horizon to 5 years increased the ICER to $[redacted][1] (+12.8%). |
| Convergence | Convergence of survival curves was incorporated in the resubmission, consistent with advice provided in the March 2022 evaluation. In the base case the parametrically extrapolated OS and PFS curves in the dostarlimab arm of the model were linearly converged to the respective curves in the SoC arm from four years, with convergence completed at six years. | Moderate. Changing the convergence to start at three years with completion at six years increased the ICER to $[redacted][1] (+10.1%) |

Source: Constructed during evaluation using Table 119, p248 of the resubmission.
*The redacted values correspond to the following ranges:*
*[1] $55,000 to < $75,000*

6.58 Table 17 summarises the results of the economic evaluation presented in the resubmission. As observed in Step 2 of the table below, extending the time horizon had an important impact on the model results despite extrapolating out to six years (rather than 10 years as in the previous submission, or 7.5 years as in the previous PSCR).

**Table 17: Results of the stepped economic evaluation (resubmission model)**

| Step and component | Dostarlimab | SoC | Increment |
|---|---|---|---|
| **Trial-based (36 months), incorporating drug and drug administration costs (Lys) [a]** | | | |
| Costs | $ | $1,120 | $ |
| LYG | 2.0219 | 1.2184 | 0.8035 |
| Incremental cost/extra LYG gained | | | $[1] |
| **Extrapolated to 6 years with convergence from 4 years and resource care use and converted QALYs** | | | |
| Costs | $ | $60,248 | $ |
| LYG (undiscounted) | 3.08 | 1.45 | 1.63 |
| QALY | 2.0145 | 0.9725 | 1.0421 |
| **Incremental cost/extra QALY gained (base case)** | | | **$**[2] |
| **Previous submission (March 2022) [b]** | | | |
| Costs | $ | $59,336 | $ |
| QALY | 2.4657 | 1.0163 | 1.4494 |
| **Incremental cost/extra QALY gained (base case)** | | | **$**[2] |

Source: Table 113, p243 of the resubmission.
ICER = incremental cost effectiveness ratio; LY = life years; QALY = quality adjusted life years; SoC = standard of care.
a A 36-month time horizon is applied in the trial-based step of the analysis. KM data is available out to 50 months for GARNET Cohort A1 (IA3 data-cut), however KM data from the base case comparator trial (ZoptEC) is available out to 38 months.
[b] Based on the model provided in the previous submission, noting revised models were provided in the previous PSCR and pre-PBAC response.
Blue shaded cell indicates values previously considered by PBAC.
*The redacted values correspond to the following ranges:*
[1] *$75,000 to < $95,000*
[2] *$55,000 to < $75,000*

6.59 Compared to the previous submission, the discounted incremental QALY gain decreased from 1.45 (over 10 years) to 1.04 (over six years). This was primarily driven by fewer QALYs estimated in the dostarlimab arm (2.47 previously, 2.01 in the resubmission). Similarly, the undiscounted life years gained (LYG) also decreased from 2.50 years (over 10 years) to 1.63 years (over six years) with the difference mainly due to fewer LYG estimated in the dostarlimab arm (4.05 previously, 3.08 in resubmission). The PSCR stated that 55% of the incremental benefits (QALYs and LYs) were accrued over the trial period, compared to 22% in the November 2021 submission. However, the ESC considered that the proportion of incremental benefits derived during the extrapolated period versus the trial period was less relevant in this case given the uncertainties with the underlying clinical data. The PSCR further claimed that the application of the more conservative assumptions in the resubmission model, together with a lower price, made the model results more robust and noted that all important sensitivity analyses showed an ICER lower than $75,000 to < $95,000 per QALY.

6.60 The ESC noted that, although the resubmission's extrapolated benefit was more conservative than the previous submission, the model still estimated a substantially larger incremental benefit for dostarlimab (1.45 LY and 1.04 QALYs over 6 years [discounted]) than the March 2022 PEM+LEN model (0.70 LY and 0.50 QALYs over 5 years [discounted]) (Table 11 pembrolizumab PSD, March 2022 PBAC meeting). The majority of the difference was in the estimated QALYs for the active treatment arm (2.01 over 6 years for dostarlimab versus 1.45 over 5 years for PEM+LEN). While the PEM+LEN model was based on the randomised controlled trial, KEYNOTE-755, which

predominantly included pMMR patients (84% of patients were pMMR and 16% were dMMR), the ESC considered the comparison in LYs and QALYs gained between the two models indicated the OS benefit estimated in the dostarlimab model was likely overestimated. The pre-PBAC response argued that overestimation of outcomes in the resubmission's model is unlikely and that differences in incremental LYs and QALYs gained estimated in the current dostarlimab model compared to the PEM+LEN model are due to differences in the magnitude of treatment effects observed in the respective clinical trial evidence bases (GARNET Cohort A1 – dMMR cohort; KEYNOTE-775 – ITT, predominantly pMMR cohort). The pre-PBAC response argued that the "higher incremental benefits estimated for dostarlimab in dMMR patients relative to PEM+LEN in all-comers are not due to any economic model assumptions which may inappropriately favour dostarlimab, but instead are explained by the differences in treatment effects between the dMMR subgroup and all-comers (ITT) population".

6.61 The approach to deriving utility values from GARNET Cohort A1 EQ-5D-5L data was fundamentally unchanged compared with the previous submission, except updated data from the more recent IA3 data-cut were used to derive utility values for the progression free (0.718) and progressed disease (0.696)[5] health states. The ESC considered this was appropriate and noted these values were slightly more conservative than in the previous submission.

6.62 A summary table of key univariate sensitivity analyses are presented in Table 18.

[5] *Note that the utility values were provided for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

**Table 18: Univariate sensitivity analyses (based on resubmission model)**

| | Incr. cost | Incr. QALYs | ICER | % change |
|---|---|---|---|---|
| **Base case** | **$** | **1.0421** | **$** [1] | **-** |
| Time horizon (base case 6 years) | | | | |
| • Within trial (27.6 months) | $ | 0.4039 | $ [2] | 66.4% |
| • 5 years | $ | 0.9266 | $ [1] | 12.8% |
| • 10 years | $ | 1.4753 | $ [3] | -30.3% |
| Utility values (base case PF=0.718; PD=0.696) | | | | |
| • GARNET Cohort A1 IA2 DC regression (PF=0.726; PD=0.684) | $ | 1.0515 | $ [1] | -0.9% |
| • Thurgar 2021 (PF=0.817; PD=0.779) | $ | 1.1843 | $ [4] | -12.0% |
| • KEYNOTE-775 ITT (PF=0.736; PD=0.700) | $ | 1.0667 | $ [1] | -2.3% |
| Discount rate (base case 5%) | | | | |
| • 3.5% | $ | 1.0771 | $ [1] | -0.7% |
| • 0% | $ | 1.1674 | $ [1] | -2.3% |
| Terminal care costs (base case $61,482; Goldsbury 2018) | | | | |
| • $54,574[a] (Goldsbury 2018; excl. PBS and MBS costs) | $ | 1.0421 | $ [1] | 0.8% |
| • $42,002 (Reeve 2018) | $ | 1.0421 | $ [1] | 2.2% |
| • $0 (excluded) | $ | 1.0421 | $ [1] | 7.0% |
| Convergence of survival curves (base case convergence between 4 to 6 years) | | | | |
| • Between 3 and 6 years | $ | 0.9500 | $ [1] | 10.1% |
| • Between 5 and 6 years | $ | 1.1314 | $ [4] | -8.2% |
| Parametric functions used for extrapolation of OS | | | | |
| • Dostarlimab OS Gompertz (base case Lognormal) | $ | 1.0979 | $ [1] | -5.5% |
| • Dostarlimab OS Exponential (base case Lognormal) | $ | 0.9804 | $ [1] | 6.8% |
| • SoC OS Weibull (base case Lognormal) | $ | 1.1013 | $ [1] | -5.8% |
| • SoC OS Loglogistic (base case Lognormal) | $ | 1.0404 | $ [1] | 0.2% |

Source: Table 119, p248 of the resubmission.
ICER = incremental cost effectiveness ratio; OS = overall survival; PD = progressed disease; PF = progression-free; PFS = progression-free survival; QALY = quality adjusted life years; SoC = standard of care.
a This figure could not be independently verified.
*The redacted values correspond to the following ranges:*
[1] *$55,000 to < $75,000*
[2] *$95,000 to < $115,000*
[3] *$35,000 to < $45,000*
[4] *$45,000 to < $55,000*

6.63 Compared to the previous submission, sensitivity analyses for the resubmission indicated that the ICER for the current model was less variable when changes were made to time horizon (e.g. a 5 year time horizon resulted in a +12.8% change in the resubmission compared to +54.3% in the previous submission), terminal care costs (e.g. removing terminal care costs altogether resulted in a +7.0% change in the resubmission compared to +13.5% in the previous submission) and changes in parametric function used for OS and PFS (e.g. using an exponential extrapolation for all OS and PFS curves resulted in a +2.0% change in the resubmission compared to +44.0% in the previous submission). These differences could be explained by the shorter time horizon in the base case and the convergence assumed.

6.64 Multivariate sensitivity analyses were conducted by the resubmission with respect to the data source used to inform the SoC arm of the model, using the studies included

in the submission's clinical evaluation (IXAMPLE2, KEYNOTE-775, and the UK RWE). The choice of SoC arm used to inform the SoC arm had a low to moderate impact on the ICER. Depending on the SoC arm selected, the resulting ICER varied by up to 14.8% (Table 19). However, the ESC considered the variation observed did not reflect the extent of uncertainty with regard to the clinical benefit as these analyses had the same limitations as the base case (e.g. informed by single arms of different studies/trials with transitivity issues, and a reliance on immature data from the single-arm GARNET study informing the dostarlimab arm).

**Table 19: Results of the multivariate sensitivity analyses (applying PFS, OS, chemotherapy regimens and treatment durations) of alternative SoC studies**

| SoC study | Incr. cost | Incr. QALYs | ICER | % Difference |
|---|---|---|---|---|
| ZoptEC (base case) | **$** | **1.0421** | **$** [1] | **-** |
| IXAMPLE2 | $ | 0.9169 | $ [1] | 14.8% |
| KEYNOTE-775 ITT | $ | 1.0624 | $ [1] | -2.1% |
| KEYNOTE-775 dMMR subgroup | $ | 1.1784 | $ [2] | -12.1% |
| UK RWE study | $ | 1.0759 | $ [1] | -2.5% |

Source: Table 121, p250 of the resubmission.
dMMR = mismatch repair deficient; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; QALY = quality adjusted life years; SoC = standard of care.
*The redacted values correspond to the following ranges:*
[1] *$55,000 to < $75,000*
[2] *$45,000 to < $55,000*

6.65 As the magnitude of the incremental benefit and the clinical significance of dostarlimab compared to SoC remain highly uncertain, the evaluation and the ESC considered that it remains unclear whether the OS benefit for dostarlimab estimated in the CUA was appropriate. The ESC noted that incorporation of the IA3 data cut in the economic evaluation, the resubmission's shorter time horizon of 6 years, and the assumption of convergence in overall survival between 4-6 years, resulted in less variability in the ICER in the sensitivity analyses presented. However, the ESC considered that there remained a high level of uncertainty in the ICER due to reliance on data from the single arm study GARNET which remained immature, and the naïve indirect nature of the clinical data applied in the model.

6.66 Acknowledging the quality of the available evidence, to address any remaining uncertainty associated with reliance on single-arm study data, the pre-PBAC response proposed a lower effective price of $ per 500mg vial, reducing the base case ICER from $55,000 to < $75,000 to $45,000 to < $55,000 per QALY. The pre-PBAC response noted that this is lower than the $75,000 to $95,000 per QALY ICER range accepted for PEM+LEN in A/R EC following PBC (para 7.13, pembrolizumab PSD, March 2022).

<u>Dostarlimab versus PEM+LEN: CMA</u>

6.67 The resubmission presented a CMA comparing dostarlimab to PEM+LEN, given the PBAC recommended PEM+LEN in patients with advanced EC who have disease

progression following prior systemic therapy regardless of biomarker status at the March 2022 PBAC meeting.

6.68 A summary of the key assumptions and components of the CMA presented in the resubmission is provided in Table 20.

**Table 20: Key components and assumptions of the cost-minimisation approach**

| Component | Claim or assumption |
|---|---|
| Therapeutic claim: effectiveness | Effectiveness for dostarlimab was assumed to be non-inferior to PEM+LEN in A/R dMMR EC following PBC |
| Therapeutic claim: safety | Safety for dostarlimab was assumed to be superior to PEM+LEN in A/R dMMR EC following PBC |
| Evidence base | Dostarlimab: GARNET Cohort A1; PEM+LEN: KEYNOTE-775 |
| Equi-effective doses | 500 mg dostarlimab Q3W = 200 mg pembrolizumab plus 289.8 mg lenvatinib Q3W, OR 7,988 mg dostarlimab = 3,195 mg pembrolizumab plus 4,630 mg lenvatinib per course of treatment (which was assumed to be 335.5 days for all treatments) |
| Duration of therapy | 335.5 days in both arms (based on the median treatment for PEM+LEN in KEYNOTE-775 in dMMR patients) |
| Direct medicine costs | Dostarlimab: $[redacted]; PEM+LEN: $[redacted] |
| Other costs or cost offsets | Administration costs:<br>Dostarlimab: $1,123; PEM+LEN: $1,645<br>Safety costs:<br>Dostarlimab: $171; PEM+LEN: $1,272 |

Source: Table 122, p253 of the resubmission.
A/R = recurrent or advanced; dMMR = mismatch repair deficient; EC = endometrial cancer; OS = overall survival PBC = platinum-based chemotherapy; PEM+LEN = pembrolizumab in combination with lenvatinib; PFS = progression-free survival; Q3W = every 3 weeks.

6.69 Equi-effective doses were determined using data from GARNET for dostarlimab and KEYNOTE-775 for PEM+LEN. Patients in GARNET received 500 mg of dostarlimab, administered as an IV infusion, every three weeks for 4 doses, followed by 1,000 mg every six weeks thereafter, in line with the dostarlimab PI. A duration of treatment of 335.5 days (the median treatment for PEM+LEN in KEYNOTE-775 in the subgroup of patients with dMMR) was used for both treatment arms. The resubmission claimed that the use of the dostarlimab median duration of treatment (238 days) would have favoured dostarlimab. This was because assuming a shorter duration of dostarlimab treatment would have reduced the number of dostarlimab doses thereby increasing the cost per dose.

6.70 However, the evaluation considered it may not have been reasonable to use the median rather than mean duration of treatment in the CMA. The ESC considered the median would underestimate the average cost per course on the PBS given the median duration of use in GARNET Cohort A1 (IA3 data-cut) was substantially shorter than the extrapolated mean estimated in the economic model (238 days versus 374 days, respectively). That is, the resubmission's use of the median, rather than the mean, duration of treatment for dostarlimab resulted in a higher price per vial of dostarlimab. The evaluation and ESC considered that it would be more appropriate to apply: a mean duration of 374 days for dostarlimab; and the mean duration for PEM + LEN that was applied in the model on which the PBAC based its March 2022 recommendation for PEM+LEN.

6.71 The PSCR stated that it would not be appropriate to estimate the net cost per patient for PEM+LEN based on the ITT cohort (irrespective of MMR status) of KEYNOTE-755, and argued that the treatment exposure of PEM+LEN was longer in dMMR patients compared with pMMR patients (354 vs 283 days, based on the truncated mean in the trial at 12 months median follow-up). The PSCR argued that the evaluator's approach would therefore underestimate the duration of PEM+LEN treatment for dMMR patients (the relevant population for the CMA). The PSCR stated if consistent follow-up periods and outcomes were considered for dostarlimab (GARNET Cohort A1 IA2 data-cut, 12.5 months follow-up) and PEM+LEN (KEYNOTE-755 dMMR 26/10/22 data-cut, 12 months follow-up), applying either the median (182 vs 336 days for dostarlimab versus PEM+LEN in dMMR patients, respectively) or truncated mean duration of therapy (286 vs 354 days for dostarlimab versus PEM+LEN in dMMR patients, respectively) would favour dostarlimab in a CMA (i.e. both the median and truncated mean durations were shorter for dostarlimab than PEM+LEN in the dMMR subgroup). The PSCR argued that it is reasonable that the same cost per day (via equivalent treatment durations derived from a dMMR population) be applied to dostarlimab and PEM+LEN as per the CMA presented in the resubmission.

6.72 However, the ESC noted that the PBAC had recommended PEM+LEN in an all-comers population regardless of MMR status. The economic model for PEM+LEN (upon which the PBAC's March 2022 recommendation was based) used the ITT results from KEYNOTE-755 (paragraph 6.54, pembrolizumab PSD, March 2022 PBAC Meeting). Analyses in the dMMR subgroup of KEYNOTE-755 were exploratory (patients with dMMR tumours comprised 16% of the total trial population, and subgroup analyses of the dMMR population were not included in the pre-specified statistical analysis plan), thus the ESC considered that any comparisons of treatment duration in pMMR versus dMMR patients would be subject to limitations. Given the price for PEM+LEN would be based on the ITT population, the ESC considered the comparisons conducted in the PSCR using the dMMR subgroup of KEYNOTE-755 were not relevant. The ESC considered that it would be appropriate for the CMA to apply (a) a mean duration of 374 days for dostarlimab (based on GARNET Cohort A1, as extrapolated in the CUA model) and (b) the mean duration of PEM+LEN as applied in the economic model on which the PBAC's recommendation was made.

6.73 The resubmission estimated equi-effective doses of 7,988 mg dostarlimab = 3,195 mg pembrolizumab plus 4,630 mg lenvatinib (which was equivalent to 500 mg dostarlimab every three weeks being equal to 200 mg pembrolizumab plus 289.8 mg lenvatinib every three weeks). The dosage of lenvatinib reflected a dose intensity equivalent to 69% (13.8/20) reported in KEYNOTE-775. Both dostarlimab and pembrolizumab were assumed to have a dose intensity of 100%.

6.74 The resubmission applied an administration cost per dose of dostarlimab and pembrolizumab to account for the cost of IV infusion. This resulted in total administration costs of $1,140.64 per course of dostarlimab, and $1,671.11 per course

of PEM+LEN, being applied in the CMA. No administration costs were attributed to lenvatinib as it is administered orally.

6.75 The resubmission claimed that given the superior safety for dostarlimab it was appropriate to include safety costs in the CMA. The resubmission claimed that due to the comparability of follow-up with KEYNOTE-775 (PEM+LEN median course of treatment 335.5 days in dMMR patients), it was appropriate to apply safety costs in the dostarlimab arm of the CMA based on the occurrence of grade ≥3 TRAEs in the IA2 data-cut of GARNET Cohort A1 rather than using the IA3 data. The resubmission limited safety costing in the CMA to particular grade ≥3 TRAEs, specifically hypertension, diarrhoea and anaemia; the evaluation noted that the use of TREAs rather than TEAEs favoured dostarlimab. The unit costs applied to the safety events in the CMA were derived from the NHCDC cost weight report (2019-20). Applying these costs to grade ≥3 TRAE reported in GARNET Cohort A1 and KEYNOTE-775 for hypertension (AR-DRG F67), diarrhoea (AR-DRG G70) and anaemia (AR-DRG Q61), total safety costs of $171.25 and $1,272.19 were applied to dostarlimab and PEM+LEN respectively in the CMA.

6.76 A summary of the CMA of dostarlimab versus PEM+LEN in A/R dMMR EC following PBC presented in the resubmission is provided in Table 21, noting this was based on published prices.

**Table 21: Results of the cost-minimisation approach**

| Row | Parameter | Input | Source / calculation |
|---|---|---|---|
| Pembrolizumab plus lenvatinib | | | |
| A | Pembrolizumab volume (mg) per course of treatment | 3,195 | Table 3B.2.4 |
| B | Pembrolizumab ex-manufacturer price per unit | $ | PBS |
| C | Pembrolizumab volume (mg) per unit | 100 | 1 * 100 mg |
| D | Pembrolizumab cost per mg | $ | B/C |
| E | Pembrolizumab drug costs per course of treatment | $ | A*D |
| F | Lenvatinib volume (mg) per course of treatment | 4,630 | Table 3B.2.4 |
| G | Lenvatinib ex-manufacturer price per unit | $ | PBS |
| H | Lenvatinib volume (mg) per unit | 300 | 30 * 10 mg |
| I | Lenvatinib cost per mg | $ | G/H |
| J | Lenvatinib drug costs per course of treatment | $ | F*I |
| K | Total drug costs per course of treatment | $ | E+J |
| L | Administration costs | $1,671 [a] | Table 3B.3.1 |
| M | Safety costs | $1,272 | Table 3B.3.4 |
| N | Total costs per course of treatment | $ | K+L+M |
| Dostarlimab | | | |
| O | Total costs per course of treatment | $ | N |
| P | Administration costs | $1,141 | Table 3B.3.1 |
| Q | Safety costs | $171 | Table 132 |
| R | Total drug costs per course of treatment | $ | O-P-Q |
| S | Volume (mg) per course of treatment | 7,988 | Table 3B.2.5 |
| T | Cost per mg | $ | R/S |
| U | Ex-manufacturer price per unit (500mg vial) | $ | T * 500 mg |

Source: Table 134, p263 of the resubmission.

[a] Administration costs were updated in evaluation to reflect the current fee of $114.20 (MBS item 13950).

## *Drug cost/patient/course*

6.77 Drug acquisition costs of dostarlimab (based on the price proposed in the resubmission) and SoC are summarised in Table 22.

**Table 22: Drug cost per patient for dostarlimab and SoC drugs (CUA)**

| | Dostarlimab | | | SoC | | |
|---|---|---|---|---|---|---|
| | GARNET | Economic model | Financial estimates | ZoptEC (doxorubicin) | Economic Model (doxorubicin) | Financial estimates (basket of comparators) |
| Recommended dose | 500mg Q3W for the first four doses, followed by 1,000mg Q6W thereafter | | | 60mg/m$^2$ Q3W | | Basket of comparators |
| Mean duration | 40.8 weeks | 53.48 weeks [b] | | 12 weeks [c] | | 12.75 weeks [e] |
| Cost/patient/course | $[redacted] [a] | $[redacted] [b] | | $[redacted] [d] | | $[redacted] [f] |

Source: sheets "Costs" and "Dostarlimab" of the economic model titled "Jemperli (dostarlimab) 2L dMMR EC CUA_July 2022" and sheets "4a Scripts – affected" and "4b Impact – affected (pub)" of the financial model titled "Jemperli (dostarlimab) 2L dMMR EC BIM_July 2022".
Q3W = every 3 weeks; Q6W = every 6 weeks.
a Price based on 9.63 administrations required for a period of 40.8 weeks ($[redacted]*first 4 doses + $[redacted]*5.63 subsequent doses). Weighted 35% public and 65% private, as used in the model and financial estimates.
b Based on economic model. The resubmission' s CMA used 48 weeks (336 days).
c Based on a median treatment duration of 4 cycles, in line with the ZoptEC trial.
d Price per total drug costs per course of doxorubicin ($[redacted] per cycle*median of 4 cycles per course). Weighted 35% public and 65% private, as used in the model and financial estimates.
e Based on a median treatment duration of 4.25 cycles, in line the UK RWE study.
f Price per total drug costs per course of carboplatin and/or doxorubicin and/or paclitaxel (either as single agent or as part of combination) considering the proportional utilisation based on the UK RWE study ($[redacted]*68% + $[redacted]*36% + $[redacted]*52% respectively per cycle*median of 4.25 cycles per course). Weighted 35% public and 65% private, as used in the model and financial estimates.

## *Estimated PBS usage & financial implications*

6.78 The previous dostarlimab submission was considered by DUSC.

6.79 The resubmission used an epidemiological approach to estimate the utilisation and financial impact of listing dostarlimab on the PBS for 2L dMMR A/R EC. A summary of the key assumptions used to calculate the financial estimates is presented in Table 23. A substantial number of changes were made compared to the previous submission, in accordance with DUSC advice.

**Table 23: Summary of data sources and parameter values applied in the utilisation and financial estimates**

| Data | Value and Source | Comment |
|---|---|---|
| **Eligible population** | | |
| Incident patients | Year 1: 3,528 increasing to year 6: 4,276. No prevalent patients considered<br>Source: Calculated by applying the average growth rate (3.9%) based on AIHW uterine cancer incidence projections for 2018-2021 to the incidence of uterine cancer in 2021 (AIHW ICD-10: C54 and C55). | Same method as previous submission. DUSC previously stated that prevalent patients should be added to the financial estimates (5.07.DUS ADV.2, March 2022). As such, the resubmission's number of eligible patients was likely underestimated.<br>The PSCR updated estimates included < 500prevalent patients. |

| Data | Value and Source | Comment |
|---|---|---|
| Proportion with each staging of disease | Stages I-II: 79.0% (638/808)<br>Stages III-IV: 21.0% (170/808)<br>Source: Gupta 2021 | This remained unchanged despite DUSC's previous advice 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, instead of being grouped with Stage IV patients (5.07.DUSC ADV.5, March 2022). These patients remained grouped with Stage IV patients, but are now assumed to include a higher proportion of patients receiving 1L PBC, with a higher rate of disease progression following 1L PBC (as discussed below). |
| Proportion with Stage I-II first recurrence | Recurrence rate: 13%<br>Source: Fung-Kee-Fung 2006 | Reasonable, consistent with previous DUSC advice (paragraph 6.72, dostarlimab PSD, March 2022 PBAC meeting). |
| Proportion receiving 1L PBC (pre and post - introduction of dostarlimab) | Proportion of Stage I-II first recurrent patients receiving 1L PBC (1L treatment patterns: 72% (90% eligible for 1L treatment; 80% of whom treated with PBC)<br>Source: Australian clinical expert opinion (n=5) provided during the Advisory Board in 2021.<br><br>Proportion of Stage III/IV patients receiving 1L PBC (1L treatment patterns): 81% (90% eligible for 1L treatment; 90% of whom treated with PBC)<br>Source: Assumption | Figure for Stage I-II patients was the same as for the previous submission, where results were based on a small survey and may therefore be uncertain (paragraph 6.72, dostarlimab PSD, March 2022 PBAC meeting). The PSCR revised estimates assumed 81% of stage I-II patients receive 1L PBC (in line with Stage III-IV patients). |
| Proportion who progress following 1L PBC | Stage I-II first recurrent patients: Derived from survival function for OS and PFS of carboplatin and paclitaxel combination treatment.<br>Source: Miller 2020.<br><br>Proportion of Stage III/I/V patients: 95%<br>Source: Based on DUSC advice. | In the previous submission, the proportion of patients who progress following 1L PBC was derived from Miller 2020 for all patients.<br>This proportion was likely underestimated (paragraph 6.72, dostarlimab PSD, March 2022 PBAC meeting). The same data set and methodology was used in the resubmission for Stage I-II patients only.<br>The progression rate for stage III-IV patients was based on DUSC comments that 'almost all' patients treated in the palliative setting will progress. Use of the survival function would be a crude measure of assessing number of patients progressing (5.07.DUSC ADV.6, March 2022). |
| Proportion with ECOG 0-1 | 70%<br>Source: Based on DUSC advice. | Reasonable. Based on DUSC advice (paragraph 6.72, dostarlimab PSD, March 2022 PBAC meeting). |
| Proportion with dMMR | 27%<br>Source: Gupta 2021. | Reasonable. Based on DUSC advice (Table 14, dostarlimab PSD, March 202 PBAC meeting). |
| **Treatment utilisation** | | |
| Grandfathered patients | [redacted]1 patients in year 1, no patients in subsequent years<br>Source: Sponsor internal estimate | |

| Data | Value and Source | Comment |
|---|---|---|
| Dostarlimab-treated population otherwise treated with chemotherapy | [redacted]%<br>Source: Australian clinical expert opinion (n=5) provided during the Advisory Board in 2021. | Appeared to be reasonable. This was tested by the resubmission (±5%) in their sensitivity analyses. |
| Utilisation among nominated basket of chemotherapies and usage for costing | Doxorubicin 107mg (150mg used)[a]: 36%<br>Paclitaxel313mg (330mg used) [a]: 52%<br>Carboplatin 630mg (900mg used)[a]: 68%<br>All assumed 12.75 weeks duration – Estimated to be 4.25 infusions per patient per year assuming three weekly cycles<br>Source: UK RWE study and clinical expert opinion. | Same values as in previous submission. DUSC considered this input could be reasonable (paragraph 6.72, dostarlimab PSD, March 2022 PBAC meeting). Duration not entirely consistent with economic model which assumed 12 weeks. |
| Mean duration of dostarlimab treatment* | 53.48 weeks<br>Source: Economic model – GARNET Cohort A1 study. | Reasonable. Figure revised from 54.37 weeks to 53.48 weeks based on revised economic model (GARNET IA3 data-cut). |
| **Costs** | | |
| Proposed medicine | **Dispensed price (effective):**<br>**Public** / **Private** / **Weighted**<br>500mg: $[redacted] / $[redacted] / $[redacted]<br>1000mg: $[redacted] / $[redacted] / $[redacted]<br>Source: Requested price, based on effective AEMP of $[redacted] (per 500mg vial). | Reasonable. Effective price was consistent with the resubmission's economic model. The effective price (500 mg vial) was reduced to $[redacted] AEMP ($[redacted] weighted DPMA) in the pre-PBAC response and updated estimates were provided. |
| Chemotherapy | **Dispensed price:**<br>**Public** / **Private** / **Weighted**<br>Doxorubicin: $[redacted] / $[redacted] / $[redacted]<br>Paclitaxel: $[redacted] / $[redacted] / $[redacted]<br>Carboplatin: $[redacted] / $[redacted] / $[redacted]<br>Source: PBS items 7222D and 4309T; 4361M and 7229L; 4567J and 7254T. | Reasonable. This was consistent with the prices and dosing used in the resubmission's economic model. |
| Infusion costs | $114.20 (MBS rebate rate of 80% used) was applied per script per patient.<br>Source: MBS item 13950 | Appropriate. |

Source: Table 135 and 136, p264-268 the resubmission.

1L = first-line; AEMP = approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; CUA = cost utility analysis; dMMR = mismatch repair deficient; DUSC = drug utilisation subcommittee; ECOG = Eastern Cooperative Oncology Group; GF = grandfathered; IHC = immunohistochemistry mismatch repair; MBS = Medicare Benefits Schedule; NZ = New Zealand; OS = overall survival; PBC = platinum-based chemotherapy; PBS = Pharmaceutical Benefits Scheme; PD = progressed disease; PFS = progression-free survival; RPBS = Repatriation Pharmaceutical Benefits Scheme; RWE = real-world evidence.

a Either as single agent or as part of combination

*The redacted values correspond to the following ranges:*

*[1] < 500*

** Note that the assumed mean duration of treatment was provided for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.80 The estimated financial impact of PBS listing dostarlimab is summarised in Table 24.

**Table 24: Estimated net financial implications of the proposed dostarlimab listing**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| **Estimation of use and financial impact of the proposed medicine (PBS and RPBS)** | | | | | | |
| Incident patients initiating dostarlimab ([redacted]%) | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 |
| Grandfathered patients moving to PBS treatment | [redacted]1 | - | - | - | - | - |
| Total patients initiating | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 |
| Total patients continuing | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 |
| Number of scripts | | | | | | |
| Initiating scripts (excluding GF) [a, b] | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]2 | [redacted]2 | [redacted]2 |
| Continuing scripts (excluding GF) [a, c] | [redacted]2 | [redacted]2 | [redacted]2 | [redacted]2 | [redacted]2 | [redacted]2 |
| GF initiating scripts [d] | [redacted]1 | - | - | - | - | - |
| GF continuing scripts [d] | [redacted]1 | - | - | - | - | - |
| Total | [redacted]2 | [redacted]2 | [redacted]2 | [redacted]2 | [redacted]2 | [redacted]2 |
| PBS/RPBS cost less co-pay | | | | | | |
| Total (eff) ($) | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 |
| **Estimation of changes in use and financial impact of other medicines (PBS and RPBS)** | | | | | | |
| Changes in number of scripts (carboplatin, doxorubicin, paclitaxel) [e] | | | | | | |
| Total | -[redacted]2 | -[redacted]2 | -[redacted]2 | -[redacted]2 | -[redacted]2 | -[redacted]2 |
| PBS/RPBS cost less co-pay (DPMA) (carboplatin, doxorubicin, paclitaxel) [f] | | | | | | |
| Total (pub/eff) ($) | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 |
| Net cost to PBS/RPBS (eff) ($) | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 |
| Net MBS costs [g] ($) | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 |
| Net cost to PBS/RPBS/MBS ($) | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 |
| **Previous submission (March 2022) effective price** | | | | | | |
| Number of patients treated | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 |
| Net cost to PBS/RPBS/MBS – submission ($) | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]4 | [redacted]4 |
| Net cost to PBS/RPBS/MBS – PSCR ($) | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 |
| Net cost to PBS/RPBS/MBS pre-PBAC response ($) | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 |
| **PSCR revised estimates** | | | | | | |
| Incident patients | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 |
| Prevalent patients | [redacted]1 | - | - | - | - | - |
| Grandfathered patients[1] | [redacted]1 | - | - | - | - | - |
| Total treated patients | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 | [redacted]1 |
| Cost of dostarlimab (effective) ($) | [redacted]4 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 |
| Cost of chemotherapy offset ($) | [redacted]5 | [redacted]5 | [redacted]5 | [redacted]5 | [redacted]5 | [redacted]5 |
| Net cost to PBS/RPBS ($) | [redacted]4 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 |
| **Pre-PBAC revised estimates** | | | | | | |
| Cost of dostarlimab (effective) ($) | [redacted]4 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 |
| Net cost to PBS/RPBS ($) | [redacted]4 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 | [redacted]3 |

Source: Tables 137, 138,139,140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, pp 269-282 of the resubmission, Table 15, 5.07 dostarlimab PBAC PSD, March 2022, Table 4 PSCR

dMMR = mismatch repair deficient; DPMA = dispensed price maximum amount; eff = effective; MBS = Medicare Benefits Scheme; GF = grandfathered; PBS = Pharmaceutical Benefits Scheme; PSCR = pre-sub-committee response; pub = published; RPBS = Repatriation Pharmaceutical Benefits Scheme.

a Estimated using the modelled mean duration of treatment for dostarlimab of 53.48 weeks, applied across initiating and continuing patient estimates to derive the initial and continuing patient years of treatment. For incident patients, 12 weeks were applicable to initiating patients (representing the maximum 12 weeks of treatment permitted under initiation restriction; first 4 cycles) and 41.48 weeks applicable to continuing patients (all cycles thereafter).

b Initiating scripts (excluding GF) = patient years of treatment × 52/3 (=17.33) scripts per year

c Continuing scripts (excluding GF) = patient years of treatment × 52/6 (=8.67) scripts per year
d Estimated scripts per patient year of treatment for the initiation and continuation phase was 8.67 (one script every six weeks). The resubmission assumed that GF patients had completed their first 4 cycles of treatment before commencing PBS-listed dostarlimab.
e Assumed [redacted]% of patients who receive dostarlimab would have received chemotherapy instead, resulting in the final proportions of patients that would substitute their respective chemotherapy agents: doxorubicin 25%, paclitaxel 36% and carboplatin 47%. (Based on the modelled mean duration of treatment for chemotherapy of ~12.75 weeks and UK RWE data)
f Calculated as the difference between the number of patients treated with dostarlimab × 10.91 services (~53.48 weeks) for incident patients or 6.69 services (40.11 weeks) for GF patients, and the number of patients treated with chemotherapy × 4.25 services (12.75 weeks).
g Assumes 80% rebate for MBS item 13950, fee amount updated during evaluation (100% = $114.20).
Blue shaded text indicates values previously considered by PBAC.
*The redacted values correspond to the following ranges:*
[1] *< 500*
[2] *500 to < 5,000*
[3] *$0 to < $10 million*
[4] *$10 million to < $20 million*
[5] *net cost saving*

6.81 The number of patients estimated to receive dostarlimab in the resubmission was higher than in the previous submission (previous submission: < 500 to < 500 patients in years 1-6). In addition to the grandfathered patients, this difference was due to the updated inputs which were predominantly in line with DUSC and PBAC recommendations for the previous submission. While the number of patients estimated to receive dostarlimab increased substantially compared to the previous submission, the estimated cost to the PBS/RPBS did not increase proportionally, predominantly due to the decrease in effective price proposed for dostarlimab.

6.82 The commentary considered that, overall, the number of eligible patients and therefore the financial estimates in the resubmission may be underestimated as:

- prevalent patients were not included in the financial estimates (though there were some grandfathered patients considered), which would have increased the number of treated patients in years 1 and 2 of the financial estimates (5.07.DUSC ADV.2, March 2022); and
- The proportion of patients receiving 1L PBC after listing of dostarlimab remains likely underestimated, despite an increase from 72% to 81% for stage III/IV patients. This was because the availability of dostarlimab would likely increase the usage of 1L PBC given that prior PBC use is part of the clinical criteria in the proposed listing to determine eligibility for dostarlimab.

6.83 The PSCR presented amended financial estimates revising the proportion of stage I-II patients receiving 1L PBC from 72% to 81% (in line with Stage III-IV patients) and including < 500prevalent patients in year 1 (as shown in Table 24). The ESC considered that these changes appeared appropriate and were in line with DUSC comments on the March 2022 dostarlimab submission. The revised estimated net cost to PBS/RPBS presented in the PSCR was $10 million to < $20 million in Year 1 and $0 to < $10 million in Year 6, with a total cost over the six-year period of $50 million to < $60 million. With the pre-PBAC revised price the estimated net cost to PBS/RPBS decreased to $10 million to < $20 million in Year 1, and $0 to < $10 million in Year 6, with a total cost over the six-year period estimated to be $50 million to < $60 million.

### *Quality Use of Medicines*

6.84 The resubmission stated that in addition to routine pharmacovigilance and risk minimisation activities, the sponsor intended to implement medical education activities and a Patient Card as a risk minimisation measure to promote safe and effective use of dostarlimab in clinical practice. The purpose of the Patient Card was to inform patients about signs and symptoms of the most common immune-related events with dostarlimab, and the main required actions to be taken if they experience any signs or symptoms of immune-related adverse reactions.

### *Financial Management – Risk Sharing Arrangements*

6.85 The resubmission indicated that the sponsor is willing to consider a risk-sharing agreement according to the base case financial estimates.

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

## 7 PBAC Outcome

7.1 The PBAC did not recommend the listing of dostarlimab for the treatment of patients with recurrent or advanced dMMR endometrial cancer who have disease progression following prior systemic therapy. The PBAC noted the clinical data were unchanged from the previous submission and considered the magnitude of the incremental benefit versus standard of care (SoC), which relied on a relatively small single arm study with immature survival data, remained uncertain. As such, the PBAC considered the cost-effectiveness of dostarlimab compared with SoC could not be reliably assessed based on the current evidence. Further, the PBAC considered that the clinical claim of non-inferior efficacy compared with pembrolizumab in combination with lenvatinib (PEM+LEN) was not sufficiently supported by the clinical data.

7.2 The PBAC considered that there is a high clinical need in this patient population but considered that its March 2022 recommendation for PEM+LEN (which was recommended on the basis of a large randomised controlled trial, KN775), when listed, would help address this clinical need. The PBAC also recalled that it had considered that the PBS listings for PEM+LEN should allow use of either component as a single agent in patients who develop an intolerance, and also allow use of pembrolizumab as a single agent in patients in whom lenvatinib is contraindicated (paragraph 7.18, pembrolizumab PSD, March 2022 PBAC meeting).

7.3 The resubmission nominated SoC comprising single-agent chemotherapy and PBC as the main comparator, which the PBAC considered to be appropriate. In addition to SoC, the resubmission nominated PEM+LEN and pembrolizumab monotherapy as near market comparators. The PBAC considered PEM+LEN was an appropriate near-market comparator, but noted it was not PBS-listed at the time of PBAC consideration.

7.4 The PBAC noted that the evidence for dostarlimab continued to be based on a cohort of patients with dMMR/MSI H endometrial cancer from an on-going, single arm, phase

I/II study of dostarlimab in patients with advanced solid tumours (the GARNET study). While the PBAC considered that dostarlimab demonstrates clinical activity in dMMR, the Committee re-iterated its previous concern that the magnitude of the incremental benefit versus SoC was unable to be reliably estimated due to:

- the evidence for dostarlimab was of relatively low quality, with only a small (n = 153) single-arm phase I/II study available, which was relatively immature (median follow up 27.6 months; median survival was not reached, with only 37% of patients having died at IA-3);
- the comparative evidence versus SoC relied on naïve indirect comparisons (between single arms of different trials) which had a high risk of bias due to differences in patient populations, and an IPTW analysis which was limited by key transitivity and methodological issues including the potential for unmeasured confounding (e.g. the two studies were conducted over different time periods).
- only a small benefit in PFS was observed in the indirect naïve comparison, which did not meet the nominated MCID of a 2.5 month absolute increase.

7.5 The PBAC considered the safety profile of dostarlimab appeared consistent with other PD-(L)1 inhibitors, and that claim of non-inferior comparative safety versus SoC was reasonable.

7.6 The PBAC considered that the claim of non-inferior efficacy versus PEM+LEN was not adequately supported by the data given: the high risk of bias of the comparison, that it was based on a naïve indirect comparison of arms from different studies; and the immaturity of the OS data.

7.7 The PBAC considered that the cost-effectiveness of dostarlimab versus SoC was unable to be reliably assessed due to the uncertain magnitude of benefit for dostarlimab, based on data from a relatively small single arm study. The PBAC acknowledged that the resubmission had applied changes to the model that were more conservative than the previous submission, and that with the lower price proposed, resulted in a lower ICER than the previous submission (the ICER in base case of the economic model submitted with the pre-PBAC response was $45,000 to < $55,000/QALY versus $55,000 to < $75,000/QALY in the previous pre-PBAC response). However, the PBAC considered that the ICER still remained unacceptably high given the level of uncertainty in the magnitude of benefit and long-term OS.

7.8 The PBAC considered that the cost-minimisation approach versus PEM+LEN was not informative as non-inferiority had not been adequately established.

7.9 The PBAC considered that the PSCR revised estimated patient numbers and utilisation appeared appropriate and changes made in the resubmission and PSCR were in line with DUSC comments on the March 2022 dostarlimab submission.

7.10 A resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway. The PBAC considered that, in the absence of a

listing for PEM+LEN there would be a high clinical need for treatments for patients with recurrent or advanced endometrial cancer and that in this case there may be a role for dostarlimab despite the limited evidence base. However, the modelled incremental benefit for dostarlimab versus SoC should account for the uncertain clinical benefit and long-term OS due to it being based on a small single-arm study, and the ICER would need to be reduced to reflect the level of uncertainty in its estimation. Alternatively, the PBAC considered that data from the RUBY trial may support an alternative clinical place for dostarlimab in earlier line EC.

7.11 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

# 8 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.

# 9 Sponsor's Comment

The sponsor had no comment.

Addendum to the November 2022 Public Summary Document:

# 10 PBAC Outcome

10.1 At its March 2022 meeting, the PBAC recommended the listing of pembrolizumab + lenvatinib (PEM+LEN) for the treatment of patients with advanced endometrial cancer who have disease progression following prior systemic therapy regardless of biomarker status.

10.2 At its November 2022 meeting, the PBAC did not recommend the listing of dostarlimab for the treatment of patients with recurrent or advanced dMMR endometrial cancer who have disease progression following prior systemic therapy. The PBAC considered that there was a high clinical need in this patient population but considered that its March 2022 recommendation for PEM+LEN (which was recommended on the basis of a large randomised controlled trial, KN775), when listed, would help address this clinical need.

10.3 Given the high clinical need for recurrent or advanced endometrial cancer, the PBAC considered a revised pricing proposal ("letter of offer") for dostarlimab out of session, in December 2022. At that time the PBAC deferred providing advice regarding whether this revised pricing proposal was acceptable as additional information was required regarding both the PEM+LEN submission and the dostarlimab submission. The Department sought the PBAC's advice at its March 2023 meeting regarding whether the cost of dostarlimab in the revised pricing proposal for the treatment of endometrial cancer is acceptably cost-effective.

10.4 The PBAC noted the sponsors' revised pricing proposal for dostarlimab of $[redacted] AEMP, resulting in ICER of $35,000 to< $45,000/QALY. The PBAC recalled that the ICER presented in the November 2022 submission was $45,000 to < $55,000/QALY. The PBAC recalled its previous advice that the magnitude of the incremental benefit versus SoC, which relied on a relatively small single arm study with immature survival data, was uncertain and noted that no additional trial data were available. The PBAC maintained that the cost-effectiveness of dostarlimab compared with SoC could not be reliably assessed based on the current evidence. On this basis the PBAC did not change its recommendation regarding dostarlimab from the November 2022 meeting. The PBAC recalled that it had reached a similar conclusion regarding pembrolizumab monotherapy for the same indication, which also relied on a small single arm study (paragraph 7.20, pembrolizumab PSD, March 2022 PBAC meeting).

**Outcome:**

Advice provided

# 11 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.

# 12 Sponsor's Comment

GSK is disappointed by the PBAC's advice to not change its decision to not recommend dostarlimab (Jemperli®) for the treatment of patients with recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen. Jemperli is currently registered by the TGA for use as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.

The PBAC has considered that the claim of superior comparative effectiveness versus current standard of care was reasonable and recognised the high clinical need for new treatments and the role Jemperli® may have in addressing this need (paragraphs 6.42 and 7.10, Dostarlimab Public Summary Document, November 2022). GSK is disappointed that the PBAC has not recommended Jemperli® under the circumstances presented in this submission, including the revised pricing proposal put forward by GSK to mitigate the uncertainty in the incremental cost-effectiveness ratio (ICER) due to reliance on single-arm study data.