

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

1 Purpose of submission

- 1.1 The Category 1 submission requested a Section 100 (Efficient Funding of Chemotherapy Program) Authority Required (STREAMLINED) listing for the treatment of advanced or recurrent (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 first submission for dostarlimab.
- 1.2 The requested basis of listing was a cost-effectiveness analysis compared to standard of care (SoC) consisting of single agent chemotherapy and platinum-based chemotherapy (PBC). Table 1 presents the key components of the clinical issue addressed by the submission.

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

Component	Description
Population	Patients with advanced or recurrent (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 for the first four doses, followed by 1,000 mg Q6W for all cycles thereafter for up to 2 years.
Comparator	Standard of care (SoC) comprising single-agent and platinum-based chemotherapies.
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, dostarlimab is superior in terms of efficacy compared to standard chemotherapy, with a manageable and non-inferior safety profile.

Source: Table 1, p19 of the submission.

A/R = recurrent or advanced; dMMR = mismatch repair deficient; EC = endometrial cancer; Q3W = every 3 weeks; Q6W = every 6 weeks

2 Background

Registration status

- 2.1 This submission was lodged under the TGA-PBAC parallel process. Dostarlimab received TGA provisional approval on 15th February 2022 for the treatment of A/R dMMR EC following PBC with 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.

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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.”

2.2 The TGA approval document stated that confirmatory trial data must be provided from the GARNET and RUBY trials.

- GARNET: The submission stated that additional patients with A/R dMMR/MSI-H EC following PBC will continue to be enrolled in Cohort A1 of GARNET.
- RUBY (NCT03981796): a randomised, double-blind phase III study of dostarlimab in combination with chemotherapy versus chemotherapy alone in patients with recurrent (first recurrence only) or primary advanced (Stage III or IV) EC, as the confirmatory study. The submission considered that longer term follow-up of GARNET was more relevant (than RUBY) for the requested PBS listing due to differences in use (monotherapy versus combination) and line of therapy (2L versus 1L).

3 Requested listing

3.1 The sponsor’s proposed listing is shown below, with changes to the restriction wording as suggested by the Secretariat shown in italics.

Name, Restriction, Manner of administration and form	Max Amt	No. of Rpts	Dispensed Price Max Amt	Proprietary Name and Manufacturer
INITIAL DOSTARLIMAB 500 mg/10 mL injection 1 x 10 mL vial	500 mg	3	\$ (public, published) \$ (private, published) \$ (public, effective) \$ (private, effective)	Jemperi, GlaxoSmithKline Australia Pty Ltd
CONTINUING DOSTARLIMAB 500 mg/10 mL injection 1 x 10 mL vial	1000 mg	3	\$ (public, published) \$ (private, published) \$ (public, effective) \$ (private, effective)	Jemperi, GlaxoSmithKline Australia Pty Ltd

Category/Program:	Section 100 (Efficient Funding of Chemotherapy)
PBS indication:	Recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer
Treatment phase:	Initial and continuing
Restriction:	Streamlined
Clinical criteria:	<p>Initial Patient must have progressed on or following prior treatment with a platinum-containing regimen, Patient must have received a prior platinum-based chemotherapy regimen for this condition, AND Patient must have an ECOG performance status of 0 or 1, AND Patient must have mismatch repair deficient (dMMR) endometrial cancer, as determined by immunohistochemistry test. AND <i>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</i></p> <p><u>Continuing</u> Patient must have previously received PBS-subsidised treatment with this drug for this condition,</p>

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	<p>AND Patient must not have <i>developed disease progression</i> while receiving PBS-subsidised treatment with this drug for this condition, AND The treatment must not exceed a <i>maximum total of 24 months in a lifetime</i> for this condition.</p>
Administrative advice:	<p>In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

- 3.2 The Pre-Sub-Committee Response (PSCR) proposed a 16.8% lower vial price than was proposed in the submission (an ex-manufacturer price of \$| per 500 mg vial was proposed in the PSCR, compared with \$| in the submission). Acknowledging the advice from Evaluation Sub-committee (ESC), the pre-PBAC response proposed an ex-manufacturer price of \$| per 500 mg vial, a 39.1% reduction compared to the price proposed in the submission.
- 3.3 The proposed clinical criteria require that a “patient must have mismatch repair deficient (dMMR) endometrial cancer (EC), as determined by immunohistochemistry test”. The submission noted that in its consideration of Medical Services Advisory Committee (MSAC) Application 1674 at the 12-13 August 2021 meeting, the PICO Advisory Sub-Committee (PASC) accepted advice from multiple sources that immunohistochemistry (IHC) mismatch repair (MMR) testing is now routine clinical and pathology practice in EC, and so considered that the basis for requiring a codependent submission was not met (Ratified PICO Confirmation – Application 1674). Similarly, the MSAC Executive agreed with the PASC conclusion to no longer require a codependent submission for IHC-based testing for dMMR in EC to help determine eligibility for PBS-subsidised medicines.
- 3.4 The requested restriction was narrower than the proposed TGA indication as the proposed TGA indication did not:
- Require patients to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. This criterion was aligned to the circumstance of use in the GARNET Cohort A1 study. The ESC considered that it may be reasonable to allow use in patients with an ECOG performance status of 2 or lower; and
 - Specify a maximum treatment period of two years. It was noted that in GARNET Cohort A1, patients may be treated for up to two years but treatment may continue beyond two years if the treating physician and the sponsor agreed that the patient would continue to benefit from the treatment.

However, these criteria were consistent with other listings for programmed cell death -1 (PD-1) or PD Ligand (PD-L1) checkpoint inhibitors listed on the PBS.

- 3.5 The proposed PBS listing did not specifically restrict use of dostarlimab to second line (2L) only. A small subset of patients (15/129 (11.6%)) with ≥ 3 prior anticancer regimens were enrolled in GARNET Cohort A1, but no subgroup results for patients with ≥ 3 prior anticancer regimens were presented. Objective response rate (ORR) in patients who received only one line of prior anticancer therapy was higher than in patients who received two or more lines of prior anticancer therapies in GARNET Cohort A1.
- 3.6 The proposed PBS listing did not specify that the patient has not received prior PD-(L)1 therapy for this condition. ESC considered that addition of this criterion would be appropriate and consistent with listings for other PD-(L)1 inhibitors.

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

4 Population and disease

- 4.1 EC is a malignancy of the endometrium, the inner lining of the uterus (uterine corpus). 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). The age-standardised incidence rate of uterine cancer in Australia has increased from 14 to 20 cases per 100,000 women from 1982 to 2021 (AIHW, 2021). In 2017, the average age at first diagnosis of uterine cancer in women was 65.1 years (AIHW, 2021). In Australia, the 5-year relative survival rate for women diagnosed with uterine cancer overall was 83.5% between 2013-2017 (AIHW, 2021) though survival rates by stages were not available. Advanced stages (stage III/IV) are associated with worse prognosis. In the UK (England), 5-year relative survival rates for Stage I, II, III and IV were 92%, 74%, 48%, and 15%, respectively for women diagnosed during 2013-2017 (Cancer Research UK, 2021b). Despite 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 MMR status, with normal (proficient) mismatch repair (pMMR) or dMMR tumours. EC is associated with dMMR in up to 33% of cases and has one of the highest rates of dMMR across all cancer types (Morona, 2020; Scarpa, 2016) although ESC noted that the rate of dMMR in advanced endometrial cancer has been reported to be lower at around 18%¹. Tumours with MMR deficiency 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

¹ Dudley J et al, *Microsatellite Instability as a Biomarker for PD-1 Blockade*. *Clin Cancer Res* February 15 2016 (22) (4) 813-820; DOI: 10.1158/1078-0432.CCR-15-1678. Available at <https://clincancerres.aacrjournals.org/content/22/4/813>

DNA MMR system (Luchini, 2019). The submission 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).

- 4.3 Dostarlimab is a humanised, monoclonal antibody of the immunoglobulin G4 isotype that binds to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2. This results in the release of inhibition of PD-1 pathway-mediated immune responses, including the anti-tumour immune response.

5 Comparator

- 5.1 The submission nominated standard of care (SoC) comprising single-agent chemotherapy and PBC as the main comparator. No specific drug(s) were nominated by the submission. However, the search strategy conducted by the submission indicated that the following treatments were included as comparators: paclitaxel; doxorubicin; carboplatin; cisplatin. The main arguments provided in support of this nomination were:

- There is currently no standard treatment for patients with A/R dMMR EC following 1L PBC. The choice of treatment in this setting is highly individualised and based on shared decision-making, taking into account the patient's clinical status, expected response, and prior and expected toxicities; and
- Single-agent chemotherapy such as doxorubicin and paclitaxel are considered the most active therapies and is particularly useful for those who are less likely to tolerate combination therapies. Re-administering carboplatin and paclitaxel may be considered in some patients if there has been a substantial amount of time since the initial administration, usually greater than six months (Concin, 2021).

- 5.2 The submission presented results from an ancillary analysis from five Gynaecologic Oncology Group (GOG) 1L trials (published between 2004-2006), which evaluated 2L treatment in 586 patients with A/R EC following primary chemotherapy (consisting of single-agent or combination, PBC and non-PBC) in which 184/586 patients (31%) received platinum-based 2L treatment and 402/586 patients (69%) received non-platinum-based 2L treatment (Moore, 2010). Moore 2010 found no significant difference in OS based on the type of 2L therapy (HR=0.92; 95% CI 0.77-1.11; p=0.392) and results remained consistent when the analysis was restricted to patients who had primary (prior) treatment with PBC (N=483).

- 5.3 From the UK real world evidence (RWE) cohort study commissioned by the sponsor, PBC accounted for the majority (67%) of 2L treatment, and a high proportion of patients used combination chemotherapy (the two most common regimens were carboplatin + paclitaxel at 27.9% and carboplatin + doxorubicin at 14.1%). The relative usage of chemotherapy from the UK RWE was used to inform the financial estimates. The only comparators considered in the clinical evidence (doxorubicin or paclitaxel)

and economic model (doxorubicin only in the base case) were single agent chemotherapies. Any differences in the distribution of 2L regimens use between the SoC studies and the Australian clinical setting may represent a potential applicability issue if there were differences in efficacy between each of the nominated therapies which comprise SoC.

- 5.4 No near market comparators were proposed in the submission, despite the use of pembrolizumab in the proposed population with the corresponding KEYNOTE-775 trial being acknowledged by the submission (though this was addressed in the PSCR). Pembrolizumab in combination with lenvatinib for the treatment of patients with advanced EC who have progressed on prior systemic therapy (irrespective of MMR status) and pembrolizumab as monotherapy for those with dMMR tumours was also scheduled to be considered during the March 2022 PBAC meeting.
- 5.5 Overall, the PBAC considered that the nominated comparator was appropriate, however noted that, should pembrolizumab ± lenvatinib be PBS listed in this indication, it would become the relevant comparator for dostarlimab.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from an organisation via the Consumer Comments facility on the PBS website. The Medical Oncology Group of Australia (MOGA) 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)², based on a single arm study.

Clinical trials

- 6.3 No head-to-head trials comparing dostarlimab with SoC were identified. Instead, indirect comparisons were constructed using the single arm GARNET study and individual comparator arms of four different trials (ZoptEC, IXAMPLE2, KEYNOTE-775 and Scambia 2020) identified in the literature search. In addition, a descriptive, non-

² Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

interventional cohort study in the UK RWE was identified via the sponsor’s internal database, outside of the systematic literature search.

6.4 A summary of the included trials and studies and the relevant arms used to inform the current submission is presented in Table 2 below.

Table 2: Summary of identified trials and studies

Study/trial	Intervention (n)	Comparator (n)
GARNET	Dostarlimab (Cohort A1 n=129)	NA
ZoptEC	Zoptarelin doxorubicin (n=256)	Doxorubicin (n=255)
IXAMPLE2	Ixabepilone (n=248)	Paclitaxel or doxorubicin (n=248)
KEYNOTE-775	Pembrolizumab + lenvatinib (n=411)	Paclitaxel or doxorubicin (n=416)
Scambia 2020	Sapanisertib + paclitaxel (n=90) Sapanisertib (n=41) Sapanisertib + serabelisib (n=20)	Paclitaxel (n=90)
UK RWE	NA	Single agent and combination platinum and non-platinum chemotherapy. (n=999)

Source: constructed during evaluation.

N = number of participants; NA = not applicable.

Shaded cells indicate evidence used to support submission.

6.5 The submission presented the following indirect comparisons:

- A naïve indirect comparison of the dostarlimab arm of the GARNET (Cohort A1) study with the SoC arms of four randomised trials: ZoptEC, IXAMPLE2, KEYNOTE-775, and Scambia 2020;
- A naïve indirect comparison of the dostarlimab arm of GARNET (Cohort A1) with the UK RWE study³; and
- An inverse probability of treatment weighting (IPTW) analysis 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)⁴.

6.6 Details of the trials and study identified by the submission’s literature search and presented in the submission are provided in the table below.

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 UK RWE. 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.

⁴ 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 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.

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Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
GARNET	<p>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).</p> <p>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 Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial.</p> <p>Nct. Study of TSR-042, an Anti-programmed Cell Death-1 Receptor (PD-1) Monoclonal Antibody, in Participants With Advanced Solid Tumors (GARNET). https://clinicaltrials.gov/ct2/show/NCT02715284.</p>	<p>Clinical Study Report dated 16 November 2020</p> <p>Full publication. <i>JAMA Oncology</i> 2020;6(11):1766-72.</p> <p>NCT record 2016.</p>
ZoptEC	<p>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</p> <p>Miller D, Scambia G, Bondarenkop I, Westermann A, Oaknin A, Oza A, et al. ZoptEC: Phase III randomized controlled study comparing zoptarelin with doxorubicin as second line therapy for locally advanced, recurrent, or metastatic endometrial cancer (NCT01767155).</p> <p>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).</p> <p>Nct. Zoptarelin doxorubicin (AEZS 108) as second line therapy for endometrial cancer (ZoptEC).</p> <p>Euctr IT. Trial with AEZS-108 in a certain stage of endometrial tumor. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2012-005546-38-IT.</p>	<p>Individual patient data 09 May 2017.</p> <p>Conference abstract 5503. <i>Journal of Clinical Oncology</i> 2018;36(15; supplement).</p> <p>Conference abstract. <i>Journal of Clinical Oncology</i> 2014;32(15).</p> <p>NCT record 2013.</p> <p>EUCTR record 2013.</p>
IXAMPLE2	<p>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.</p> <p>Nct. A Study of Ixabepilone as Second-line Therapy for Locally Advanced, Recurrent, or Metastatic Endometrial Cancer.</p> <p>https://clinicaltrials.gov/show/NCT00883116.</p> <p>Euctr IT. A Phase III Open Label, Randomized, 2 Arm Study of Ixabepilone Administered Every 21 Days Versus Paclitaxel or Doxorubicin Administered Every 21 Days in Women with Advanced Endometrial Cancer Who Have Previously Been Treated with Chemotherapy. - ND.</p> <p>http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-007167-16-IT.</p>	<p>Full publication <i>Gynecologic Oncology</i> 2015;138(1):18-23.</p> <p>NCT record 2009.</p> <p>EUCTR record 2009.</p>
KEYNOTE-775	<p>Makker V, Colombo N, Herráez AC, Santin A, Colomba E, Miller D, et al. A multicenter, open-label, randomized, phase III study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab versus treatment of physician's choice in patients with advanced endometrial cancer.</p> <p>Makker V, Herraез AC, Aghajanian C, Fujiwara K, Pignata S, Penson RT, et al. A phase 3 trial evaluating efficacy and safety of lenvatinib in combination with pembrolizumab in patients with advanced endometrial cancer.</p> <p>Lorusso D, Colombo N, Herraез AC, Santin A, Colomba E, Miller DS, et al. Health-related quality of life (HRQoL) in advanced endometrial cancer (aEC) patients (pts) treated with lenvatinib plus pembrolizumab or treatment of physician's choice (TPC).</p>	<p>Conference abstract <i>Gynecologic Oncology</i> 2021;162:S4.</p> <p>Conference abstract <i>Journal of Clinical Oncology</i> 2019;37.</p> <p>Conference abstract <i>Journal of Clinical Oncology</i> 2021;39(15 SUPPL).</p>

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Trial ID	Protocol title/ Publication title	Publication citation
	<p>Nct. Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer (MK-3475-775/E7080-G000-309 Per Merck Standard Convention [KEYNOTE-775]). https://clinicaltrials.gov/show/NCT03517449.</p> <p>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.</p> <p>Makker V, Colombo N, Casado Herraез A, et al. Randomized phase 3 study of lenvatinib plus pembrolizumab for advanced endometrial cancer: subgroup analysis of patients with DNA mismatch repair-deficient tumors. Study 309/KEYNOTE-775.</p>	<p>NCT record 2018.</p> <p>Conference presentation Society of Gynecologic Oncology. Virtual Annual Meeting on Women's Cancer 2021.</p> <p>Conference abstract 43/ID O002 presented at: 2021 IGCS Annual Global Meeting; August 30-September 2, 2021; virtual. Plenary 1.</p>
Scambia 2020 (NCT02725268)	<p>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.</p> <p>Nct. Phase 2 Study of MLN0128, Combination of MLN0128 With MLN1117, Paclitaxel and Combination of MLN0128 With Paclitaxel in Women With Endometrial Cancer. https://clinicaltrials.gov/show/NCT02725268.</p>	<p>Conference abstract <i>Journal of Clinical Oncology</i> 2020; 38, (15 SUPPL).</p> <p>NCT record 2016.</p>

Source: Table 17, pp58-60 of the submission.

6.7 The key features of the included trials and studies are summarised in Table 4.

Table 4: Key features of the included evidence

Study, N ^a	Study Design	Interventions ^b	Population	Main Outcomes	Use in modelled evaluation	Median duration of follow-up (months)
GARNET Cohort A1 & Cohort A2 (N=290)	Single-arm, open-label, Phase I/II	Dostarlimab (Cohort A1 n=129; Cohort A2 n=161): 500 mg Q3W for the first 4 cycles followed by 1,000 mg Q6W for all subsequent cycles. IA-3 data cut-off provided with PSCR: Cohort A1, n = 153	A/R EC following PBC (Cohort A1: dMMR; Cohort A2: pMMR)	OS, ORR, PFS	Yes, in the base case	Cohort A1: 12.5 (ITT) ^{d,e} or 16.3 (PES); Cohort A2: N/R (ITT) or 11.5 (PES) IA-3 data cut-off provided with PSCR: Cohort A1 (PES) 29.4 months
ZoptEC N=511	Open-label, randomised, Phase III	Doxorubicin (n=255): 60 mg/m ² by intravenous bolus injection or 1-hour IV infusion, on Day 1 of 21-day (3-week) cycles.	Locally advanced, recurrent, or metastatic EC, following platinum plus taxane therapy.	OS, ORR, PFS	Yes, in the base case	Planned for 12 ^f , but IPD indicated a duration of 26.7 ^g
IXAMPLE 2 N=496	Open-label, randomised, Phase III	Paclitaxel/doxorubicin (n=248) Paclitaxel: 175 mg/m ² given IV over 3 hours, or per institutional guidelines but not exceeding 3 hours, every 21 days OR Doxorubicin: 60 mg/m ² given IV per institutional guidelines every 21 days, depending on the prior therapy received.	Locally advanced, recurrent, or metastatic EC, following PBC.	OS, ORR, PFS	Used in sensitivity analyses	Planned for 6 ^h
KEYNOTE-775 N=827	Open-label, randomised, Phase III	Paclitaxel/doxorubicin (n=416) Paclitaxel: 80 mg/m ² given IV QW, three weeks out of every four OR Doxorubicin: 60 mg/m ² given IV Q3W (up to a maximum cumulative dose of 500 mg/m ²).	Advanced, recurrent or metastatic EC, following PBC.	OS, ORR, PFS	Used in sensitivity analyses	10.7 ⁱ
Scambia 2020 N=241	Open-label, randomised, Phase III	Paclitaxel (n=90): 80 mg/m ² , IV, weekly on Days 1, 8 and 15 of 28-day cycles.	Advanced, recurrent, or persistent EC, following PBC.	OS, ORR, PFS	Not used	14.4 ^j
UK RWE N=45,494	Descriptive, non-interventional	Single agent or combination chemotherapy regimens including (but not limited to) carboplatin, cisplatin, paclitaxel, doxorubicin and gemcitabine. Dosages not reported.	Patients diagnosed with between 01/01/2013 and 31/12/2018 in England ^c .	OS, TTNT, TTD	Used in sensitivity analyses	GARNET-like loose cohort: 27.4; GARNET-like strict cohort: 27.0

Source: Table 18, p63 of the submission.

A/R = advanced or recurrent; dMMR = mismatch repair deficient; EC = endometrial cancer; IPD = individual patient data; ITT = intention-to-treat; N/A = not applicable; N/R = not reported; ORR = objective response rate; OS = overall response; PBC = platinum-based chemotherapy; PES = primary efficacy set; PFS = progression-free survival; RWE = real world evidence; TTD = time to treatment discontinuation; TTNT = time to next treatment.

^a Total patients in the intent-to-treat population included in all arms of the study/trial.

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b The complete arms of the SoC trials were as follows: ZoptEC: zoletarelin doxorubicin vs. doxorubicin; IXAMPLE2: ixabepilone vs. paclitaxel or doxorubicin; KEYNOTE-775: lenvatinib plus pembrolizumab vs. paclitaxel or doxorubicin; Scambia 2020: Paclitaxel plus sapanisertib vs. sapanisertib vs. sapanisertib plus serabelisib vs. paclitaxel.

c Inclusion and exclusion criteria were applied to the population by the submission to derive GARNET-like cohorts (i.e. advanced or recurrent disease, and confirmed receipt of prior platinum-doublet therapy).

d Indicated by the submission (p104) and used in the submission's economic model, but could not be verified during the evaluation

e Note that the median duration of follow-up based on ITT was 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.

f It was expected that approximately 500 patients will be enrolled during an estimated 24-month recruitment period and will then be followed for 12 months to observe a total of approximately 384 death events (ZoptEC protocol, p60)

g Note that the median duration of follow-up was presented specifically 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.

h An interim analysis was conducted after 176 deaths had been observed or 300 patients had been randomized and followed for 6 months, whichever came earlier (IXAMPLE2 publication McMeekin 2015, p3).

i For pts randomized to treatment of physician's choice (i.e. paclitaxel or doxorubicin) based on data cutoff of October 26, 2020 (Makker 2021). Median follow-up for the treatment of physician's choice arm of the dMMR subgroup was 8.8 months based on data cutoff of October 26, 2020 (Makker 2021b).

j Based on data cutoff of 30 July 2019 (Scambia 2020)

6.8 GARNET is an on-going, single-arm, open-label, first-in-human phase I/II study of dostarlimab in patients with advanced solid tumours. The GARNET study had several patient cohorts. Of these, Cohort A1 and A2 were most relevant to the submission:

- Cohort A1 (n=129 in submission data-cut; n = 153 in PSCR data-cut): dMMR/MSI-H EC patients who have progressed on or after platinum doublet therapy; and
- Cohort A2 (n=161): pMMR/microsatellite stable (MSS) EC patients who have progressed on or after platinum doublet therapy.

Other cohorts (E, F, and G) involved other types of solid tumours (such as non-small cell lung cancer and primary peritoneal cancer) and were therefore not included as clinical evidence in the submission.

6.9 The UK RWE was a sponsor-commissioned, descriptive, non-interventional, study using data available through the National Cancer Registration and Analysis Service (NCRAS) in England. The study included patients diagnosed with A/R EC between 2013 and 2018. From study entry, patients were followed prospectively to the occurrence of events of interest, such as treatment or death. Only selected results were provided.

6.10 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.

6.11 None of the trials that informed SoC restricted patient enrolment by MMR status (MMR status was only assessed in GARNET and KEYNOTE-775). However, the submission considered that this would not affect the exchangeability of the studies as it claimed MMR status was not a treatment effect modifier for chemotherapy, based on systematic literature reviews and the fact that the OS confidence interval in dMMR

and pMMR patients treated with SoC in KEYNOTE-775 overlapped (see paragraph 6.18). Overall, the evidence presented by the submission to support the assertion that MMR status was not a treatment effect modifier for chemotherapy was inconsistent and limited by the heterogeneity of studies included in the literature reviews and sample size issues. The ESC noted that 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 given the limited evidence available from KEYNOTE-775 tended to indicate that patients with dMMR status may have had poorer outcomes with chemotherapy than those with pMMR.

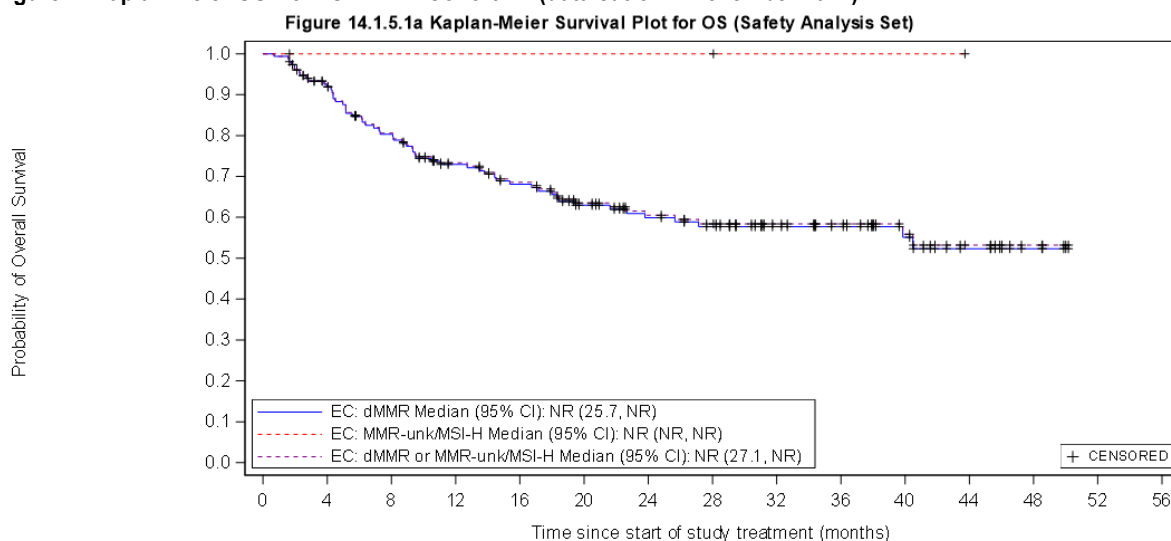
- 6.12 In GARNET Cohort A1 and A2, the primary efficacy set (n=105 in the data-cut provided in the submission), defined as all patients who received any amount of study drug with measurable disease at baseline who had the opportunity for at least 24 weeks of tumour assessment at the time of analysis, was used for the assessment of the primary outcome of ORR instead of the ITT population (n=129). It was unclear if the trade-off between a longer duration of follow-up for a smaller sample size would provide more reliable data or if the loss of statistical power would introduce more uncertainty in the result, however the ITT results were more favourable for dostarlimab compared to the primary efficacy set results for OS and PFS.
- 6.13 The submission also defined a main analysis set from GARNET Cohort A1 which was used to inform the IPTW with doxorubicin. The main analysis set (N=325, with 92 patients from GARNET Cohort A1 and 233 from ZoptEC) was constructed in an attempt to balance baseline characteristics between GARNET Cohort A1 and ZoptEC by excluding patients who did not have an ECOG score of 0 or 1, had previously received more than one prior platinum-based therapy, or had a follow up greater than 36 months in ZoptEC.

Comparative effectiveness

Key outcomes presented by the submission

- 6.14 The PSCR presented OS data from a more recent data-cut of GARNET, interim analysis 3 (IA-3) which was based on a data cut-off date of 1 November 2021, as shown in the figure below.

Figure 1: Kaplan-Meier OS from GARNET Cohort A1 (data cut-off 1 November 2021)



Number of patients at risk

EC: dMMR	150	130	110	93	82	68	58	50	37	31	21	13	5	0	0
EC: MMR-unk/MSI-H	3	2	2	2	2	2	2	2	1	1	1	0	0	0	0
EC: dMMR or MMR-unk/MSI-H	153	132	112	95	84	70	60	52	38	32	22	13	5	0	0

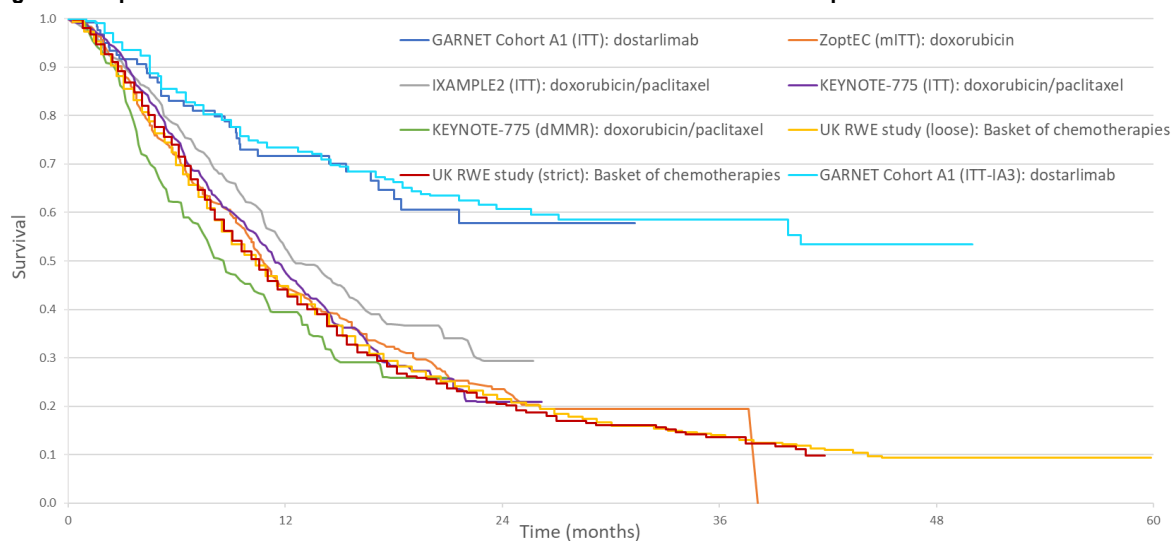
Medians presented in months.

Source: Figure 1, p2 of the PSCR.

CI = confidence interval; dMMR = mismatch repair deficient; EC = endometrial cancer; MSI-H = Microsatellite Instability High.

6.15 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 5.

Figure 2: Kaplan-Meier overall survival curves from GARNET Cohort A1 and comparator studies



Source: Figure 2, p2 of the PSCR

dMMR = mismatch repair deficient; IA-3 = interim analysis 3; ITT = intention-to-treat; mITT = modified intention-to-treat; RWE = real-world evidence.

Note: OS curves were generated via the digitising of KM curves reported. OS KM curves were not available for Scambia 2020.

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 5: Summary of deaths in the relevant arms of included trials and studies

Trial	Analysis set	N	Deaths, n (%)	Censored, n (%)	Median, months (95%CI)
Dostarlimab					
GARNET Cohort A1	ITT	129	36 (27.9)	93 (72.1)	NR (18.4, NR)
	PES	105	35 (33.3)	70 (66.7)	NR (17.1, NR)
	MAS ^a	92	31 (33.7)	61 (66.3)	NR (17.2, NR)
GARNET Cohort A1 IA-3 data cut	ITT	153	57 (37.3)	N/R	NR (27.1, NR)
GARNET Cohort A2	ITT	161	76 (47.2)	85 (52.8)	16.8 (12.9, 21.4)
	PES	156	75 (48.1)	81 (51.9)	16.8 (12.9, 21.4)
GARNET Cohort A1 & A2	ITT	290	112 (38.6)	178 (61.4)	21.3 (16.8, 26.4)
	PES	261	110 (42.1)	151 (57.9)	18.5 (16.0, 26.4)
SoC					
ZoptEC (doxorubicin) ^b	mITT	249	188 (75.5)	61 (24.5)	10.8 (9.8, 12.6)
	MAS ^c	233	177 (76.0)	56 (24.0)	11.04 (10.0, 13.01)
IXAMPLE2 (paclitaxel or doxorubicin)	ITT	248	98 (39.5)	150 (60.5)	12.3 (10.7, 15.4)
KEYNOTE-775 (paclitaxel or doxorubicin)	ITT	416	245 (58.9)	171 (41.1)	11.4 (10.5, 12.9)
	dMMR	65	42 (64.6)	23 (35.4)	8.6 (5.5, 12.9)
	pMMR	351	203 (57.8)	148 (42.2)	12.0 (10.8, 13.3)
Scambia 2020 (Paclitaxel)	ITT ^d	90	58 (64)	32 (35)	12.7 months (9.8, 19.6)
UK RWE (basket comparator)	GARNET like loose	999	739 (74.0)	N/R	10.3 (9.2, 11.1)
	GARNET like strict	501	368 (73.5)	N/R	10.3 (9.0, 11.1)

Source: Tables 46&49, pp 115&121 of the submission and Table 36, p161 of the GARNET Clinical Study Report; Sheet "Table 3" in the "UK RWE_Final results tables" excel workbook.

CI = confidence interval; dMMR = mismatch repair deficient; ES = Efficacy Set; ITT = intention to treat; MAS = main analysis set (for adjusted indirect comparison); mITT = modified intention to treat; N/R = not reported; NR = not reached; PES = primary efficacy set; pMMR = mismatch repair proficient.

a 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

b The anonymised ZoptEC IPD was licensed to the sponsor for indirect comparison purposes (unpublished data). The use of the mITT set for OS was inconsistent with Table 2.4.2 which stated that the ITT (N=255) set was to be used. The submission may have chosen to use the mITT set (N=249; which excluded 6 patients in the doxorubicin arm of ZoptEC who did not receive a dose), given access to IPD. Given this, the values for censored and median OS were unable to be verified during the evaluation using the information provided by the submission.

c 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.

d The values for events and censored were updated during the evaluation based on reported results that became available subsequent to the submission (clinicaltrials.gov: NCT02725268).

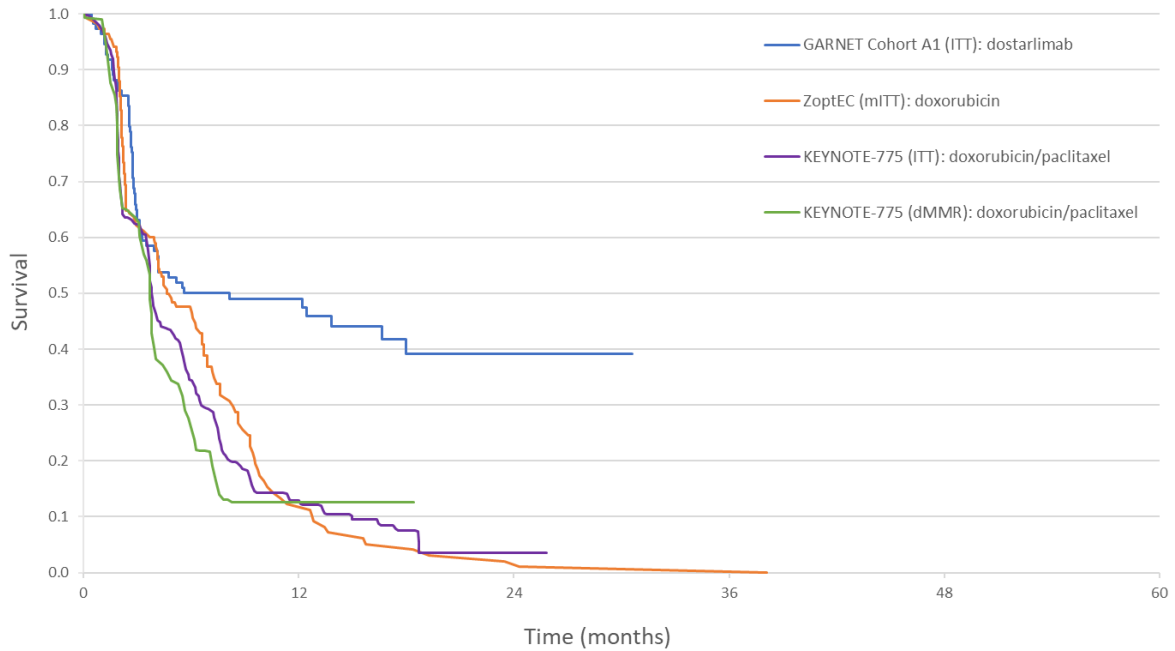
6.16 Median OS was not reached (NR) in the GARNET Cohort A1 ITT set (95% confidence interval (CI): 27.1, NR). The lower confidence limit for median OS of 27.1 months was higher than the upper confidence limit on SoC arms in the included studies (11.1-19.6 months, including the UK RWE).

6.17 The updated data from IA-3 had a median follow-up of 29.4 months for the PES (versus 16.3 months for the IA-2 data cut-off). The PSCR stated "Overall, the efficacy and safety of dostarlimab observed at IA-3 analyses, remained consistent with prior data cuts (IA-2, IA-1), with the benefit of increased sample size and extended follow-up" and "the magnitude of dostarlimab survival benefit is improving over time, with the

continued plateauing of the KM plot in the latest data cut-off (IA-3).” However, the ESC considered that the updated data did not clearly indicate a longer-term plateau in OS, noting that median OS was not reached (only 37% of patients had died at IA-3) and the relatively small number of patients at risk toward the tail of the Kaplan-Meier curve (refer to Figure 1). Further, the lack of comparator arm made it difficult to determine whether any plateau would also be observed with SoC. The pre-PBAC response argued that median OS not being reached was evidence in support of plateauing survival and that this plateauing of survival was observable out to four years whereas OS curves from available SoC studies demonstrate a median OS of between 8.6-12.7 months. The pre-PBAC response also noted that no additional data from GARNET Cohort A1 is expected until Q3 2024.

- 6.18 The submission noted the 3.4-month difference in median OS reported between the dMMR (8.6 months; 95% CI: 5.5, 12.9) and pMMR (12.0 months; 95% CI: 10.8, 13.3) subgroups in patients treated with SoC in KEYNOTE-775. However, the submission claimed that as the upper confidence limit of the dMMR subgroup exceeded the median reported for the pMMR subgroup, it was uncertain if the observed difference was generalisable to a real difference in outcomes between dMMR and pMMR patients in A/R EC following PBC.
- 6.19 The overlay of Kaplan-Meier OS curves from GARNET Cohort A1 and the included trials showed initial overlap of curves, before crossing in favour of dostarlimab from approximately 3 months. The submission highlighted the consistency of OS across the SoC cohorts, which the submission claimed provides a greater degree of certainty to the naïve indirect comparison. The lack of confidence intervals in the Kaplan-Meier curves may have led to misleading visual interpretations of the certainty of the incremental difference between different arms in the included studies and trials.
- 6.20 The PFS Kaplan-Meier curves and key PFS outcomes of the relevant arms of the included trials and studies are presented in Figure 3 and Table 6. Not all of the identified trials provided Kaplan-Meier curves for PFS.

Figure 3: Kaplan-Meier progression-free survival curves from GARNET Cohort A1 and comparator trials



Source: Figure 27, p123 of the submission.

dMMR = mismatch repair deficient; ITT = intention-to-treat.

Note: PFS curves were generated via the digitising of KM curves reported. PFS KM curves were not available for IXAMPLE2, Scambia (2020) or the UK RWE.

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 6: 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)
Dostarlimab					
GARNET Cohort A1	ITT ^{a,b}	129	60 (46.5)	69 (53.5)	5.6 (3.3, 18.0)
	PES	105	57 (54.3)	48 (45.7)	5.5 (3.2, NR)
	MAS ^c	92	49 (53.3)	43 (46.7)	8.1 (3.2, NR)
GARNET Cohort A1 IA-3 data cut	PES	143	83 (58.0)	60 (42.0)	6.0 (4.1, 18.0)
GARNET Cohort A2	ITT ^{a,b}	161	N/R	N/R	N/R
	PES	156	128 (82.1)	28 (17.9)	2.7 (2.6, 2.8)
GARNET Cohort A1 & A2	ITT	290	N/R	N/R	N/R
	PES	261	185 (70.9)	76 (29.1)	3.0 (2.8, 4.0)
SoC					
ZoptEC (doxorubicin) ^d	mITT	249	148 (59.4)	101 (40.6)	4.7 (4.1, 6.6)
	MAS ^c	233	138 (59.2)	95 (40.8)	4.9 (4.1, 6.6)
IXAMPLE2 (paclitaxel or doxorubicin)	ES	223	162 (72.6)	61 (27.4)	4.0 (2.7, 4.3)
KEYNOTE-775 (paclitaxel or doxorubicin)	ITT	416	286 (68.8)	130 (31.3)	3.8 (3.6, 4.2)
	dMMR	65	48 (73.8)	17 (26.2)	3.7 (3.1, 4.4)
	pMMR	351	238 (67.8)	113 (32.2)	3.8 (3.6, 5.0)
Scambia 2020 (Paclitaxel)	ITT	90	N/R	N/R	3.7 (2.3, 4.3)
UK RWE (basket comparator)	GARNET like loose	999	N/R	N/R	N/R
	GARNET like strict	501	N/R	N/R	N/R

Source: Tables 46&49, pp 115&121 of the submission; Table 35, p157 of the GARNET Clinical Study Report; Table 11, p 25 of the Final Report – ZoptEC Analysis.

CI = confidence interval; dMMR = mismatch repair deficient; ES = Efficacy Set; ITT = intention to treat; MAS = main analysis set (for adjusted indirect comparison); mITT = modified intention to treat; N/R = not reported; NR = not reached; PES = primary efficacy set; pMMR = mismatch repair proficient.

^a The values reported for the ITT set of GARNET for were not able to be verified during the evaluation using information provided by the submission.

^b Note that the ITT 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.

^c 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.

^d The anonymised ZoptEC IPD was licensed to the sponsor for indirect comparison purposes (unpublished data). The 95%CI for median PFS was not able to be verified during the evaluation using information provided by the submission.

6.21 A median PFS of 5.6 months (95% CI: 3.3, 18.0) was reported in the ITT population, and 5.5 months (95% CI: 3.2, NR) in the primary efficacy set (6.0 months (95% CI: 4.1, 18.0) in IA-3) of GARNET Cohort A1⁵. Comparatively, the SoC arms of the included studies reported median PFS of 3.7-4.9 months, with the lower and upper 95% CI ranging from 2.7 (in IXAMPLE2) to 6.6 months (in ZoptEC), respectively. Given the lower 95% CI of all dostarlimab arms (irrespective of cohort or analysis set) was lower

⁵ Note that the ITT 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.

than 9.1 months (6.6+2.5 months), the nominated MCID of an absolute increase in PFS of 2.5 months was not met.

- 6.22 The overlay of Kaplan-Meier PFS curves from GARNET Cohort A1 and the SoC arms of the included trials showed initial overlap of curves before crossing in favour of dostarlimab from approximately six months onwards (this is discussed further in paragraph 6.53). Similar to that observed in the Kaplan-Meier OS curves, dMMR patients (from KEYNOTE-775) appeared to have a higher risk of progression/death.
- 6.23 ORR was also reported as a key outcome in the submission. An ORR of 44.8% (95%CI: 35.0, 54.8) was reported for dostarlimab patients in the primary efficacy set of GARNET Cohort A1. Updated data from IA-3 indicated an ORR of 45.5% (95% CI: 37.1, 54.0). Among patients achieving a response, median duration of response (DOR) was not reached over trial follow-up (range: 2.63, 28.09 months in the submission data-cut). The submission noted that the lower confidence limit for ORR on dostarlimab of 35.0% was higher than the upper confidence limit on SoC across the included trials (18.4%-26.5%). It was unclear whether these results were clinically meaningful, and an MCID for ORR (or DOR) was not nominated by the submission.

Secondary outcomes

- 6.24 The results of the EQ-5D-5L from GARNET were not provided in the submission's clinical evaluation and could not be extracted during the evaluation as these were not reported in the Clinical Study Report provided. The submission however, utilised the EQ-5D-5L results collected in GARNET A1 in their economic model. This is described in Table 8.

Subgroup analyses

- 6.25 The submission presented a comparison of the outcomes from GARNET Cohort A1 (dMMR A/R EC) and Cohort A2 (pMMR A/R EC), which it claimed demonstrated the predictive effect of MMR status with respect to the efficacy of dostarlimab in A/R EC following PBC. Overall, it was plausible that MMR status may be a treatment effect modifier for dostarlimab, as patients in GARNET Cohort A1 appeared to have better outcomes compared to those in Cohort A2, though this was based on a comparison of two open label cohorts with no formal statistical testing. As noted by the TGA evaluator (TGA Clinical Evaluation Report, p93), "overall, these findings indicate that patient selection based on dMMR versus MMR-proficient status for EC identified and enriched for a population more likely to respond to dostarlimab". However, it was also noted that "a proportion – albeit much smaller – of patients with MMR-proficient tumours also had responses which were durable".

IPTW adjusted indirect comparison

- 6.26 The submission presented an IPTW adjusted indirect comparison using IPD from a matched main analysis set of patients (n=325) from GARNET Cohort A1 (n=92) and the doxorubicin arm of ZoptEC (n=233) (see paragraph 6.13). A Cox proportional hazards model with stabilised-IPTW was utilised to estimate the OS hazard ratio for

dostarlimab versus doxorubicin and reported a statistically significant improvement in OS for dostarlimab versus doxorubicin (HR=0.41; 95% CI: 0.28, 0.61; p<0.0001). This would meet the proposed MCID of 25% improvement in survival. No information regarding the median duration of follow up of patients in the main analysis set was provided.

- 6.27 A sensitivity analysis was conducted by the submission on the safety analysis set which included all ITT patients (N=378; GARNET=129 and ZoptEC N=248) with adjusting stabilised IPTW to assess whether this would affect the OS results. Dostarlimab was found to be associated with a statistically significant improvement in OS versus doxorubicin (HR=0.40; 95%CI: 0.28, 0.58; p<0.0001) in the safety analysis set.
- 6.28 Due to differences in the timepoints for tumour assessments between the GARNET and ZoptEC studies (12 weeks after the first dostarlimab dose and every 6 weeks thereafter in GARNET vs every 9 weeks during ongoing treatment then every 3 months thereafter in ZoptEC), descriptive statistics rather than comparative analyses were presented for all secondary endpoints (PFS, ORR, DOR, and time to deterioration in QoL). The results of the naïve side by side indirect comparison of secondary endpoints suggested that compared to doxorubicin, dostarlimab was associated with longer PFS, higher ORR, longer DOR, and longer time to deterioration of QoL.
- 6.29 There were several limitations associated with the IPTW analysis:
- The clinical trial periods of the two studies were different with GARNET being conducted between 2017-2020, whereas ZoptEC was conducted between 2013 and 2016;
 - The nature of the study design in which patient cohorts from separate studies (designed for different purposes) were used, which had the possibility of introducing selection bias (bias by confounding, including the potential for unmeasured confounding given only those factors collected in both trials on the same evaluation visit schedule were utilised). These may not have been accounted for given the Cox proportional hazards regression models with IPTW could only achieve balance on known factors, and the exchangeability assumption was not verifiable and the number of covariates for IPTW may be limited by the sample size;
 - As biomarker testing was not performed in the ZoptEC trial, matching to GARNET was not feasible to include only patients that were dMMR/MSI-H. Given that the scientific literature is mixed on the prognostic value of dMMR/MSI-H with existing chemotherapies, it was unknown whether the use of all patients in ZoptEC would under or overestimate the patient response to treatment in comparison to dostarlimab;
 - the point estimate for PFS of GARNET Cohort A1 in the main analysis set (8.1 months, 95% CI 3.2, NR) was substantially greater than the ITT population (5.6 months, 95% CI 3.3, 18.0). The commentary considered this may be evidence that the methodology of the IPTW favoured dostarlimab and there may have been unmeasured confounding. The PSCR stated that “the difference in median PFS

observed in the IPTW analysis (as compared to the ITT analysis) is primarily an artefact of the observed plateauing occurring very close to the median patient rather than being due to the IPTW being biased in favour of dostarlimab”; and

- It was unclear why patients with more than 36 months of follow-up (n=4) were excluded from ZoptEC. By excluding patients with longer survival from the comparator, the analysis likely unreasonably favoured dostarlimab.

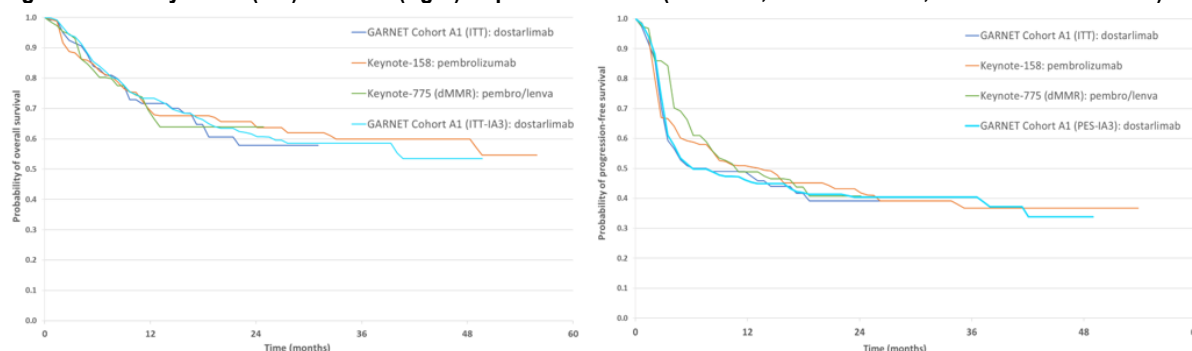
6.30 Overall, the IPTW data supported the naïve side by side comparison presented by the submission which suggested that dMMR patients with A/R EC treated with 2L dostarlimab were likely to have longer OS compared to patients treated with 2L SoC. However, given the significant limitations of the IPTW, the magnitude of benefit was highly uncertain.

Comparison versus pembrolizumab

6.31 The PSCR provided an overlay of OS and PFS KM curves of dostarlimab versus pembrolizumab monotherapy and combination therapy with pembrolizumab and lenvatinib (Figure 4). The PSCR stated that “similar OS and PFS trends were observed across all interventions, suggestive of a comparable efficacy”. Median OS was not reached in any of the interventions. The PSCR stated that tumour assessment in GARNET (week 12 after first dose then every 6 weeks in the first year then every 12 weeks) was performed more frequently in the first 12 months when compared to KEYNOTE-158 (every 9 weeks in the first year then every 12 weeks) and KEYNOTE-775 (every 8 weeks until primary analysis then every 12 weeks), which may potentially bias (measurement bias) the results against dostarlimab.

6.32 The PBAC noted that the comparison had not been independently evaluated as it was provided with the PSCR.

Figure 4: Overlay of OS (left) and PFS (right) Kaplan-Meier data (GARNET, KEYNOTE-158, KEYNOTE-775 dMMR)



Source: Figure 6, p7 of the PSCR

Note: OS and PFS curves were generated via the digitising of KM curves reported in: GARNET CSR; GARNET IA-3; O'Malley 2022, Makker 2021b. PFS KM plot based on ITT safety analysis set for IA-3 is not available from the initial topline results.

dMMR = mismatch repair deficient; IA-3 = interim analysis 3; ITT = intention-to-treat; OS = overall survival; Pembro+Lenva = pembrolizumab + lenvatinib; PES = primary efficacy set; PFS = progression-free survival

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.

Comparative harms

6.33 A summary of safety outcomes reported across the included trials/studies is presented in Table 7.

Table 7: Summary of safety from included studies

Intervention	Dostarlimab			Doxoru bicin	Paclitaxel or doxorubicin			Pacli- taxel
	GARNET Cohort A1	GARNET Cohort A2 ^a	ZoptEC ¹	IXAMPL E2	KEYNOTE-775		Scambia 2020	
Analysis set	Safety IA-2	Safety IA-3	Safety	Safety	Safety	Safety	dMMR safety	Safety
N	129	153	161	249	239	388	63	87
Any TEAE, %	95.3	99.3	100.0	NR	95.4	99.5	98.4	97.7
TEAE resulting in treatment discontinuation, %	11.6	15.7	9.9	15.3	15.5	8.0	6.3	N/R
Treatment related TEAEs leading to discontinuation, %	3.9	8.5	6.8	N/R	N/R	5.7	N/R	N/R
Treatment related TEAEs, %	63.6	70.6	70.8	N/R	90.0	93.8	N/R	N/R
SAE, %	34.1	37.9	46.6	30.1	29.3	30.4	N/R	26.4
Treatment-related SAEs, %	9.3	11.8	8.1	NR	12.0	14.2	N/R	N/R
Treatment-related Grade ≥3 TEAEs, %	13.2	17.6	19.3	N/R	N/R	59.0	N/R	N/R
Grade ≥3 TEAE, %	48.1	56.9	55.9	78.3	N/R	72.7	73.0	54
Anaemia	14.7	N/R	9.9	15.3	N/R	14.7	N/R	12
Abdominal pain	5.4	N/R	3.7	1.6	N/R	N/R	N/R	N/R
Neutropenia	1.6	N/R	0.0	45.0	N/R	25.8	N/R	3
Leukopenia	1.6	N/R	0.0	18.1	N/R	N/R	N/R	N/R
White blood cell count decreased	0.0	N/R	0.6	8.0	N/R	N/R	N/R	N/R
Fatigue	0.8	N/R	4.3	5.6	N/R	3.1	N/R	5
Nausea	0.0	N/R	4.3	5.2	N/R	1.3	N/R	N/R

Source: Table 40, p109 of the submission, Makker 2022 (Supplementary Table S11, S12, S15); GARNET IA-3 Table 14.3.1.1a

ITT = intention-to-treat; N/R = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event; N/R = not reported
1 The anonymised ZoptEC IPD was licensed to the sponsor for indirect comparison purposes (unpublished data).

^a Extracted from Tables 54&14.3.1.5a, p198 of the submission and GARNET TLFs_data-listings

Note: Safety outcomes were not available from the UK RWE study.

6.34 Similar proportions of patients treated with dostarlimab and SoC experienced any grade treatment emergent adverse event (TEAEs) (dostarlimab= 95.3-100.0%; SoC= 95.4-99.5%), adverse events (AEs) resulting in treatment discontinuation (dostarlimab= 9.9-15.7%; SoC= 6.3-15.5%), while serious adverse events (SAEs) were observed to be higher (dostarlimab = 34.1-46.6%; SoC= 26.4-30.1%). The ESC noted there was an increase in AEs with longer exposure to dostarlimab, for example treatment-related Grade ≥3 TEAEs increased from 13.2% to 17.6% at IA-2 and IA-3, respectively. The PBAC noted that Grade ≥3 TEAEs were generally slightly lower in GARNET Cohort A1 than in the SoC studies (48.1-56.9% vs 54-78.3%) and Grade ≥3

treatment related TEAEs were also lower in GARNET than KN775 (13.2-19.3% vs 59.0%). The pre-PBAC response also noted that MOGA considered dostarlimab to be less toxic than chemotherapy. The PBAC considered that this was consistent with other PD-(L)1 inhibitors.

- 6.35 The submission noted the most common grade ≥ 3 TEAE experienced on dostarlimab in GARNET was anaemia, with similar occurrence reported for SoC across included trials (dostarlimab= 9.9-14.7%; SoC= 12-15.3%). The submission acknowledged that on the whole, the inconsistent reporting of disaggregated safety outcomes across included SoC studies made it challenging to determine the specific differences in grade ≥ 3 TEAEs between dostarlimab and SoC.
- 6.36 The most frequently reported TEAEs ($\geq 15\%$) in patients with dMMR EC in GARNET Cohort A1 were nausea, diarrhoea, anaemia, fatigue, asthenia, constipation, vomiting, abdominal pain, cough, arthralgia, urinary tract infection, and back pain. These TEAEs were mild or moderate in severity in most patients for whom the TEAEs were reported.
- 6.37 The PBAC noted that, based on other PD-(L)1 inhibitors, AEs for dostarlimab would be expected to be different from AEs for chemotherapy.
- 6.38 The TGA evaluator (TGA Clinical Evaluation Report) commented that “to date, only 515 patients have received dostarlimab monotherapy at the proposed dosage to provide safety data in support of the registration of dostarlimab”, with a median treatment duration of 20 weeks, and 132 participants exposed for at least 48 weeks. It was noted that “there were no new safety signals across the larger population and there were no deaths considered treatment-related.” The TGA evaluator (TGA Clinical Evaluation Report) concluded that “while the adverse event profile is largely consistent with other much more widely studied PD-1 inhibitors, it cannot be stated at this time that there is sufficient longer-term data or characterisation of dostarlimab to warrant full registration.” Further, the Delegate’s Overview states “The clinical evaluation highlighted limitations in the safety information, pointing specifically to a limited understanding of immune-related cardiac events and limits to the immunogenicity data so far in the study program”.

Benefits/harms

- 6.39 The PSCR stated the proportion of patients alive at two years of follow up is approximately 60% with dostarlimab compared to approximately 20% with SoC (Figure 2), indicating that for every 100 patients treated with dostarlimab, an additional 40 patients will be alive at 2 years. However, the ESC considered that an adequate assessment of the magnitude of any OS benefit was not possible with the available data.

Clinical claim

- 6.40 The submission described dostarlimab as superior in terms of effectiveness compared with SoC in patients with A/R dMMR EC following PBC.
- 6.41 The PBAC agreed with ESC that, while it was likely reasonable to conclude that dostarlimab has superior efficacy compared with SoC, an adequate assessment of the magnitude of the OS benefit was not possible with the available data because:
- the evidence was of relatively low quality, with only a small single-arm phase I/II study of dostarlimab available, which was compared with the SoC arms of randomised trials. The submission also conducted an adjusted IPTW analysis, however this was limited by key methodological and transitivity issues including the nature of the study design as well as potential unobserved confounding, the likelihood of which was increased due to incomplete matching;
 - The immaturity of the data from GARNET Cohort A1 (median survival was not reached, with only 37% of patients having died at IA-3) limited the ability to interpret any median OS benefit from any of the indirect comparisons presented. This also increased uncertainty regarding the durability of any benefit with dostarlimab; and
 - 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.
- 6.42 The ESC further noted that no randomised studies were in progress that would provide greater uncertainty of the magnitude of the benefit of dostarlimab in the requested patient population.
- 6.43 With regard to safety, the submission described dostarlimab as non-inferior compared to SoC. The ESC considered this claim was uncertain due to the inconsistent reporting of disaggregated safety outcomes across the included studies. A relatively low number of patients have been exposed to the current dostarlimab dose and with limited follow-up. Longer follow-up will be required to provide more certainty regarding the relative safety.
- 6.44 The PBAC noted the limitations of the safety data available for dostarlimab and considered that the claim of non-inferior comparative safety may be reasonable, and safety outcomes are likely to be different for dostarlimab compared with chemotherapy.

Clinical claim versus pembrolizumab

- 6.45 The PSCR stated that “similar OS and PFS trends were observed across all interventions, suggestive of a comparable efficacy” between dostarlimab, pembrolizumab monotherapy and pembrolizumab in combination with lenvatinib. The PBAC noted that the comparison was naïve and based on limited data and considered that a comparison with pembrolizumab to support the claim of non-inferiority would require full independent evaluation.

Economic analysis

- 6.46 The submission presented a stepped economic evaluation of dostarlimab versus SoC in A/R dMMR EC following PBC. The type of economic evaluation presented was a cost-utility analysis. The dostarlimab arm of the model was informed by the GARNET Cohort A1 study, whilst the SoC arm of the model was informed by the doxorubicin arm of ZoptEC in the base case.
- 6.47 The submission claimed that the ZoptEC trial was selected for use in the base case because the trial had both longer follow-up and IPD available for the estimation of survival. The pre-PBAC response further argued that the use of ZoptEC to inform the SoC arm of the model was conservative as it included pMMR patients. The remaining SoC trials and study presented in the submission’s clinical evaluation were used to inform the SoC arm in sensitivity analyses presented by the submission (apart from Scambia 2020, which did not report any Kaplan-Meier data and had insufficient data to populate the SoC arm of the model).
- 6.48 Table 8 presents a summary of the model structure used in the economic evaluation presented in the submission.

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Table 8: Summary of model structure and rationale

Component	Summary
Interventions compared	Dostarlimab compared with doxorubicin. This was inconsistent with the basket of comparators used in the submission's financial estimates based on the UK RWE study.
Type of analysis	Cost-utility analysis
Time horizon	10 years in the model base case, shortened to 7.5 years in the PSCR. This compares with a median follow-up of 12.5 months in the GARNET Cohort A1 study (29.4 months in IA-3 provided in the PSCR) and median follow-up of 26.7 months in the ZoptEC trial. Given the low five-year survival rate for Stage IV EC of 15% (67% of patients in GARNET Cohort A1 had Stage IV disease), the fact that these patients have already failed PBC treatment, and the immature OS data from GARNET, a time horizon of 7.5 years may be optimistic. The time horizon was shortened to 6.25 years in the pre-PBAC response base case.
Outcomes	Life years gained, quality-adjusted life years gained
Methods used to generate results	Partitioned survival model
Health states	Three health states: progression-free; progressed disease; dead
Cycle length	21 days.
Allocation to health states	Dostarlimab arm: KM estimates for PFS and OS from GARNET Cohort A1 were used for the first 19 cycles, followed by extrapolation of PFS and OS. SoC arm: KM estimates for PFS and OS from ZoptEC were used for the first 39 cycles, followed by extrapolation of PFS and OS. Parametric functions were fitted to the trial data. The selection was based on statistical goodness of fit, visual fit to KM curves and clinical plausibility. The lognormal function was chosen for OS and PFS extrapolation in both arms.
Utilities	EQ-5D-5L scores from GARNET Cohort A1 were used to derive utility estimates based on an Australian scoring algorithm (Viney 2011). The predicted utility scores by progression status estimated using the regression analysis were applied to equally for both the dostarlimab and SoC arms of the economic model. Inappropriately no confidence intervals were reported. PFS health state utility: 0.726 ^a PD health state utility: 0.684 ^a Alternative utilities from Thurgar 2021, which was a published study of dostarlimab compared to paclitaxel (based on IXAMPLE2), were tested in a sensitivity analysis. Thurgar 2021 used EQ-5D data from KEYNOTE-158 for women with dMMR/MSI-H metastatic EC. PF utilities of 0.817 (range 0.797-0.836) and PD utilities of 0.779 (range 0.699-0.859) was used in Thurgar 2021.
Discount rate	█% per annum
Software package	Microsoft Excel

Source: Table 75, p157 of the submission.

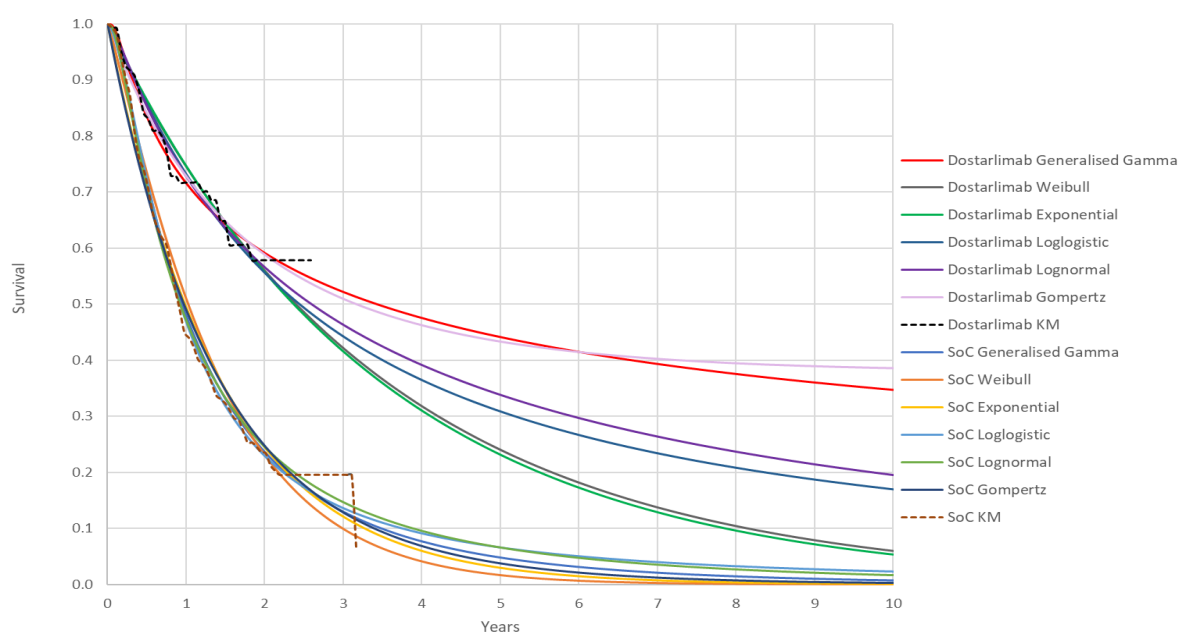
EC = endometrial cancer; KM = Kaplan-Meier; OS = overall survival; PD = progressed disease; PFS = progression-free survival; RWE = real world evidence.

a 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.

- 6.49 The ITT population of GARNET Cohort A1 was used for the dostarlimab arm in the economic model, even though the primary efficacy set and the main analysis set were also available. This may have favoured dostarlimab as results of the ITT set were observed to be the most favourable for dostarlimab, but it was unclear how much this would impact the incremental cost effectiveness ratio (ICER).
- 6.50 The fitted parametric survival curves for OS for dostarlimab and SoC are presented in Figure 5 (noting that the Kaplan-Meier data in the figure is based on the data-cut

presented in the submission, IA-2). The submission selected the lognormal function for OS and PFS extrapolation in both arms as this function predicted a moderate plateauing of survival (unlike the exponential and Weibull functions), provided more conservative long-term OS estimates than the generalised gamma and Gompertz functions, and was a better statistical fit than the log-logistic function. All functional forms had reasonable fit with the Kaplan-Meier data (from IA-2) based on both the Akaike information criterion and Bayesian information criterion (all criterion scores were within 5 points).

Figure 5: Parametric survival curves: Dostarlimab OS (GARNET Cohort A1 – dostarlimab arm, IA-2) and SoC OS (ZoptEC – doxorubicin arm)



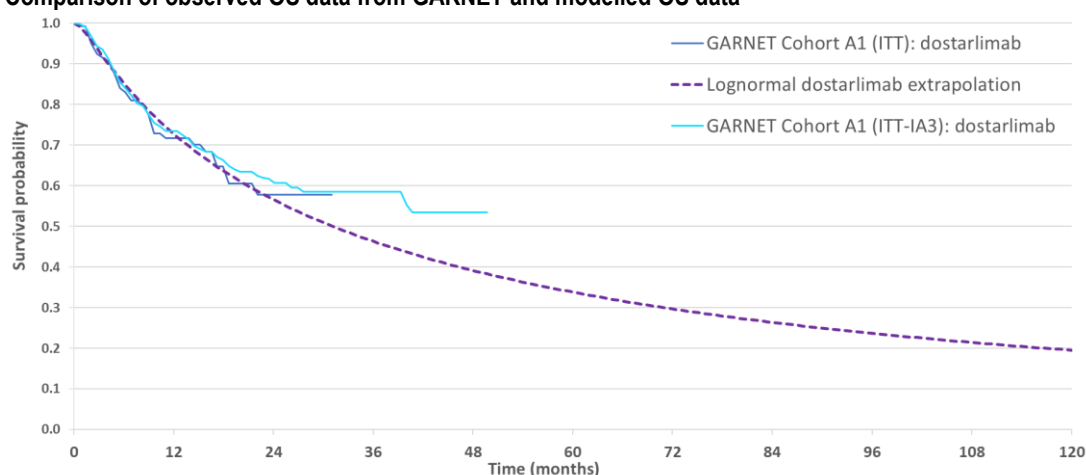
Source: Constructed during the evaluation using figures from sheets “OS_GARNET” and “OS_ZoptEC” of the economic model titled “Jemperli (dostarlimab) 2L dMMR EC CUA”.

- 6.51 There was a large variance in OS extrapolations with different functions in the dostarlimab arm and this variance became larger, the longer the extrapolation. The choice of extrapolation function for OS for dostarlimab was a driver of the model, but the choice of extrapolation function of the SoC arm had a much smaller impact on the ICER, as the number of patients remaining alive when the extrapolation was used was lower and therefore inherently had higher certainty.
- 6.52 ESC noted that there was a large separation between the dostarlimab and SoC extrapolated curves from early in the model, with a large difference continuing throughout the model time horizon (7.5 years in the PSCR). ESC noted that the extrapolation function selected by the submission (lognormal) estimated a 22% difference in the proportion of patients alive in each arm at 7.5 years (with 25% of patients alive in the dostarlimab arm and 3% in the SoC arm). ESC considered that such

a large difference in OS over time, and the implied ongoing treatment benefits associated with dostarlimab over SoC, were not adequately justified by the clinical data presented. Use of the exponential function in both arms (for OS) resulted in a more conservative difference in the proportion of patients alive at 7.5 years (a difference of 10.6%, with 11.1% of patients alive in the dostarlimab arm and 0.5% in the SoC arm).

- 6.53 As noted above, the submission selected the lognormal function for OS and PFS extrapolation in both arms as this function predicted a moderate plateauing of survival. The submission argued that as PFS in GARNET Cohort A1 plateaued from approximately six months, indicating a reduction in the rate of disease progression over this period, and given that disease progression was the primary reason for death in GARNET Cohort A1 (86%, 31/36, of deaths in GARNET Cohort A1 were attributed to progressive disease), the PFS plateau would be expected to translate into a subsequent plateauing of OS. However, the submission also stated that in GARNET Cohort A1, “(PFS) data beyond six months would rely heavily on the tail of the dataset which is associated with increasingly uncertain estimates”. As such, the assumption of an OS plateau based on the PFS plateau may not be justified.
- 6.54 The PSCR and pre-PBAC response argued that there is a continued plateauing of OS in the Kaplan-Meier plot in the latest data cut-off (IA-3) and that the economic model understates the OS plateauing effect observed in the longer term based on the latest data cut-off. However, ESC considered that the updated data did not clearly indicate a longer-term plateau in OS, as outlined in paragraph 6.17.

Figure 6: Comparison of observed OS data from GARNET and modelled OS data



Source: Figure 5, p5 of the PSCR

Note that the Kaplan Meier plots and fitted curve depicted in Figure 6 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 Overall, ESC considered that the OS extrapolation was uncertain due to the relatively short follow-up in GARNET Cohort A1 (even with the extended follow-up provided in the PSCR) and the concerns (raised in the ‘Comparative effectiveness’ section) which

meant that an adequate assessment of the magnitude of any OS benefit was not possible. ESC considered that the lack of complete convergence in OS curves within the model time horizon for patients receiving dostarlimab versus SoC may not be clinically plausible. This favoured dostarlimab by producing higher quality-adjusted life-years (QALY), and reduced costs of terminal care, than would have been observed under a scenario where complete convergence in OS occurred. The majority of the benefit modelled was derived during the extrapolated period. ESC noted that a higher degree of convergence could be achieved through use of the log-logistic, exponential or Weibull functions in both arms for OS, though none of these extrapolations led to complete convergence within the model time horizon (e.g. using the exponential function, the difference in the proportion of patients alive would be 10.6% at 7.5 years and 5% at 10 years).

- 6.56 ESC considered that an alternative way to reduce these uncertainties could be through the use of a shorter time horizon. While the PSCR reduced the time horizon from 10 years to 7.5 years, the ESC considered that 5 years may be more appropriate.
- 6.57 ESC noted that the model applied a one-off terminal care cost of \$█ for every death, based on Goldsbury 2018. However, ESC noted that these costs were averages of several kinds of cancers, of which none were endometrial. It is unclear whether this average would be representative of endometrial cancer costs. Further, ESC noted that the terminal care cost was based on the 12 months prior to death and considered this may result in double counting as some of these costs would have accrued in the progressed health state.
- 6.58 Given that there was no clinical evidence to support that dostarlimab would improve survival in the long term, and the issues with the cost estimate itself, ESC considered that it would be more reasonable to assume that there would be no difference in terminal care costs between the treatment arms, or that a small difference may accrue due to the impact of discounting. ESC noted the impact of including terminal care costs on the ICER is driven by the difference in surviving proportions at the end of the model time horizon but ultimately this cost should accrue to all patients in both treatment arms. The pre-PBAC response argued that the complete removal of terminal care costs would bias results against dostarlimab as “dostarlimab’s superior survival would result in reduced discounted terminal care costs, even with OS curves convergence, due to the impact of discounting”.
- 6.59 Table 9 summarises the key drivers of the economic model, based on the base case proposed in the PSCR.

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Table 9: Key drivers of the model

Description	Method/Value	Impact Base case ICER in PSCR = \$ [REDACTED]
Extrapolation function for OS	Parametric functions were fitted to the trial data to extrapolate respective survival curves to the model time horizon.	High, favoured dostarlimab or SoC depending on the choice of extrapolation. The choice of extrapolation (applied to both the dostarlimab and the SoC arms) for OS had a large impact on the ICER (e.g. 31% increase using exponential).
Time horizon	Base case time horizon was 10 years, which was reduced to 7.5 years in the PSCR. ESC considered that a shorter time horizon of 5 years may be more appropriate given the immature OS data from GARNET. The majority of benefit modelled was derived during the extrapolated period. A longer OS extrapolation was also associated with increased uncertainty for dostarlimab arm (see paragraph 6.51).	High, favoured dostarlimab. Changing the time horizon to 5 years increased the ICER to \$ [REDACTED] (31%).
Terminal care costs	Base case assumed a once off terminal care cost of \$ [REDACTED] for every death, based on Goldsbury 2018. However, ESC considered that, as treatment with dostarlimab delays rather than prevents death, the application of terminal care costs is uncertain unless a significant difference in the 'cured' population is clinically plausible as the terminal care costs will also (eventually) be incurred by patients treated with dostarlimab, albeit not captured in the time horizon.	Removing terminal care costs increased ICER by 18%. Moderate and favours dostarlimab.
Utility	Base case utility for PF (0.726) and PD (0.684). A higher utility value for PD or PF led to a lower ICER, and a lower utility value for PD or PF led to a higher ICER, irrespective of the incremental difference between PF and PD. Sensitivity analyses using values from Thurgar 2021, which were numerically higher than the base case (PF = 0.817, PD = 0.779) but with a smaller incremental difference between states, were tested by the submission.	Using values from Thurgar 2021, reduced the ICER by 11.5%. Moderate impact. Possibly favoured SoC. However, should the utility in the Australian population be numerically lower than calculated by the submission (which was based on a non-Australian population and mapped therefore carried uncertainty), may favour dostarlimab.

Source: Table 117&118, pp209-210 of the submission.

PD = progressed disease; PF = progression free; OS = overall survival; SoC = standard of care

6.60 Table 10 summarises the results of the economic evaluation presented in the submission.

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Table 10: Results of the stepped economic evaluation (submission and PSCR)

Step and component	Dostarlimab	SoC	Increment
Step 1: trial-based (24 months) costs and outcomes (LYs)			
Costs	\$	\$	\$
LY gained	1.4693	1.0429	0.4264
Incremental cost/extra LYG gained			\$
Step 2: time horizon extended to 10 years (LYs)			
Costs	\$	\$	\$
LY gained	3.4930	1.4530	2.0400
Incremental cost/extra LYG gained			\$
Step 3: transformation of outcomes to QALYs			
Costs	\$	\$	\$
QALY	2.4657	1.0163	1.4494
Incremental cost/extra QALY gained			\$
Step 4: incorporation of health care resource use costs (QALYs)			
Costs	\$	\$	\$
QALY	2.4657	1.0163	1.4494
Incremental cost/extra QALY gained (base case)			\$
Revised base case presented in PSCR (7.5 year time horizon, removal of half-cycle correction for costs, 16.8% reduction to AEMP)			
Costs	\$	\$	\$
QALY	2.2050	0.9924	1.2126
Incremental cost/extra QALY gained (base case)			\$

Source: Table 112, p206 of the submission.

ICER = incremental cost effectiveness ratio; LY = life years; QALY = quality adjusted life years; SoC = standard of care.

- 6.61 The extrapolation from 24 months to a ten year time horizon substantially reduced the ICER (by 79%). In the submission base case, the largest contributors to the incremental cost in the model were the drug acquisition costs (+108.6% of incremental cost), followed by terminal care costs (-13.5% of incremental cost). The incremental life years (LYs) and quality adjusted life years (QALYs) accrued in the progression-free health state accounted for more than half (61.6%) of the total incremental outcome between the two treatment groups. A difference in PFS was modelled despite the naïve comparison of dostarlimab and SoC not supporting a PFS benefit given the MCID was not met, which may not be reasonable.
- 6.62 The PSCR proposed a revised base case with a time horizon of 7.5 years and no half cycle correction for dostarlimab drug costs, which increased the ICER to \$75,000 to < \$95,000 per QALY. To re-align the ICER with the submission base case (\$55,000 to < \$75,000 per QALY), the PSCR proposed a 16.8% reduction in the price.
- 6.63 A summary table of key univariate and multivariate sensitivity analyses, based on the PSCR model, are presented in Table 11.

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Table 11: Results of univariate and multivariate sensitivity analyses based on PSCR model

Variable	Base case	Scenario	Δ cost (\$)	Δ QALY	ICER (\$)	% change
Base case (PSCR)				1.2126	■ ²	-
Univariate analyses						
Time horizon	7.5 years	5 years		0.8867	■ ⁴	+31.2%
Discount rate	■% ¹	■% ¹		1.2686	■ ²	-3.4%
		■% ¹		1.4177	■ ²	-11.1%
Extrapolation function	OS: lognormal; PFS: lognormal	OS extrapolations loglogistic		1.1159	■ ²	+11.4%
		OS extrapolations exponential		0.9917	■ ⁴	+31.1%
		OS extrapolations Weibull		1.0423	■ ⁴	+23.7%
Terminal care costs	Goldsbury 2018 (\$■)	Assumed to be \$0		1.2126	■ ⁴	+18.3%
		Assumed to be halved (\$■)		1.2126	■ ²	+9.1%
Utility	GARNET Cohort A1 (PF: 0.726, PD: 0.684)	Thurgar 2021 (PF: 0.817; PD: 0.779)		1.3695	■ ²	-11.5%
		10% lower utility in progressed disease health state		1.1758	■ ²	+3.1%
No difference in PFS modelled				1.1637	■ ²	+0.6%
Multivariate analyses						
Time horizon and extrapolation function	Time horizon of 7.5 years and extrapolations of OS: lognormal	5 years and OS extrapolations log logistic		0.8372	■ ⁴	+42.3%
		5 years and OS extrapolations exponential		0.7945	■ ⁵	+53.9%
Time horizon and terminal care costs	Time horizon of 7.5 years and terminal care costs applied (\$■)	5 years and terminal care costs assumed to be \$0		0.8867	■ ⁵	+60.8%
		5 years and terminal care costs assumed to be halved (\$■)		0.8867	■ ⁵	+46.0%
Extrapolation function and terminal care costs	Extrapolations of OS: lognormal and terminal care costs applied (\$■)	OS extrapolations: log logistic + terminal care costs assumed to be \$0		1.1159	■ ⁴	+28.5%
		OS extrapolations: exponential + terminal care costs assumed to be \$0		0.9917	■ ⁴	+44.6%

Source: Table 117&118, pp209-210 of the submission.

KM = Kaplan-Meier; ICER = incremental cost effectiveness ratio; OS = overall survival; PD = progressed disease; PF = progression-free; PFS = progression-free survival; QALY = quality adjusted life years.

The redacted values correspond to the following ranges:

¹ Commercially sensitive

² \$55,000 to < \$75,000

³ \$25,000 to < \$35,000

⁴ \$75,000 to < \$95,000

⁵ \$95,000 to < \$115,000

6.64 ESC noted a multivariate sensitivity analysis in which terminal care costs were removed and the time horizon was reduced to 5 years resulted in an ICER of \$95,000 to < \$115,000/QALY (61% increase). ESC also noted another analysis in which terminal care costs were removed and with exponential extrapolation of both arms for OS (increased convergence) resulted in an ICER of \$75,000 to < \$95,000/QALY (45% increase) but noted that this scenario still led to a 10.6% difference in the proportion of patients alive in each arm at 7.5 years. Complete convergence of both

arms for OS over 7.5 years could not be tested using the current structure of the model.

- 6.65 ESC noted that inclusion of terminal care costs had an increasing impact with shorter time horizons, and a decreasing impact when the difference in surviving proportions at the end of the model time horizon was reduced.
- 6.66 To address the uncertainty associated with long-term survival estimates the pre-PBAC response provided a revised model including survival curve convergence (between 5 and 7.5 years) and removal of terminal care costs. As convergence would require structural changes to the model, the pre-PBAC response also conducted an alternative analysis with a 6.25 year time horizon (no convergence) and removal of terminal care costs. Maintaining an ICER of \$55,000 to < \$75,000/QALY, the two approaches resulted in similar AEMPs (\$ per 500 mg vial for the first approach, and \$ for the alternative approach). The sponsor proposed a reduced effective AEMP of \$ per 500 mg vial, based on a 6.25 year time horizon and no terminal care costs.
- 6.67 Multivariate sensitivity analyses were conducted by the submission 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 10.5% (see Table 12).

Table 12: Results of the multivariate sensitivity analyses (applying PFS, OS, chemotherapy regimens and treatment durations) of alternative SoC studies

Study	Total Costs (\$)	Total QALYs	Incr cost vs dostarlimab (\$)	Incr QALY vs dostarlimab	ICER vs dostarlimab (\$)	% change
GARNET Cohort A1 (dostarlimab)		2.4657	-	-	-	-
ZoptEC (base case)		1.0163		1.4494	²	-
IXAMPLE2		1.1460		1.3197	²	10.5%
KEYNOTE-775 ITT		0.9590		1.5067	²	-4.7%
KEYNOTE-775 dMMR subgroup		0.8575		1.6082	²	-10.5%
UK RWE study		0.9736		1.4921	²	-4.0%

Source: Table 121, p211 of the submission.

dMMR = mismatch repair deficient; ICER = incremental cost effectiveness ratio; Incr = incremental; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; RWE = real world evidence; QALY = quality adjusted life years; SoC = standard of care.

The redacted values correspond to the following ranges:

² \$55,000 to < \$75,000

Cost-minimisation versus pembrolizumab monotherapy

6.68 The PSCR claimed that dostarlimab is “of similar efficacy and safety” to pembrolizumab monotherapy and presented a cost-minimisation approach in the dMMR population. The PSCR estimated that the equi-effective doses were:

- 1,000 mg dostarlimab every 6 weeks; and
- 400 mg pembrolizumab every 6 weeks (i.e., calculated as 200 mg pembrolizumab administered every 3 weeks multiplied by 2).

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The PSCR stated this was based on dosing in the pivotal studies and an assumption that both regimens would have the same treatment duration given the common mechanism of action (i.e., PD-1 inhibitor).

- 6.69 The PSCR did not account for differences in relative dose intensity, administration costs, adverse event costs or disease management costs.

Drug cost/patient/course

- 6.70 Drug acquisition costs of dostarlimab and SoC are summarised in Table 13 below, using the updated price per vial proposed in the pre-PBAC response.

Table 13: Drug cost per patient for dostarlimab and SoC drugs

	Dostarlimab			SoC		
	GARNET	Economic model	Financial estimates	ZoptEC (doxorubicin)	Economic Model (doxorubicin)	Financial estimates (basket of comparators)
Mean dose	500 mg Q3W for the first four doses, followed by 1,000 mg Q6W thereafter			60 mg/m ² Q3W		Basket of comparators
Mean duration	40.8 weeks	54.4 weeks ^b		12 weeks ^c		12.75 weeks ^e
Cost/patient/course	\$ ^a	\$ ^b		\$ ^d		\$ ^f

Source: sheets “Costs” and “Dostarlimab” of the economic model titled “Jemperli (dostarlimab) 2L dMMR EC CUA” and sheets “4a Scripts – affected” and “4b Impact – affected (pub)” of the financial model titled “Jemperli (dostarlimab) 2L dMMR EC BIM”.

Q3W = every 3 weeks; Q6W = every 6 weeks.

a Price based on 9.63 administrations required for a period of 40.8 weeks (\$^a*first 4 doses + \$^a*5.63 subsequent doses). Weighted 35% public and 65% private, as used in the model and financial estimates.

b As updated in the pre-PBAC response (removal of half-cycle correction, 6.25 year time horizon and removal of terminal care cost, and incorporating lower AEMP), undiscounted.

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 (\$^d 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 (\$^f*68% + \$^f*36% + \$^f*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

- 6.71 This submission was considered by DUSC.
- 6.72 The submission 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 14.

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Table 14: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value and Source	Comment
Eligible population		
Incident patients	Year 1: 3,395 increasing to Year 6: 4,115 Source: Calculated by applying the average growth rate (3.9%) of uterine cancer incidence projections for 2018-2021 (AIHW) to the incidence of uterine cancer in 2021.	DUSC noted that prevalent patients (those diagnosed prior to year 1 of the estimates who recur and become eligible for dostarlimab) should also have been included. The pre-PBAC response argued that these patients were implicitly accounted for given the prevalent pool of Stage I/II patients diagnosed from 2016 onwards (prior to year 1) was included (adjusted for timing as disease recurrence was expected to occur over time).
Proportion of uterine cancer reported as EC	95.0% Source: NZ Ministry of Health 'Cancer: New registrations and deaths 2013'.	DUSC considered this source appeared reasonable.
Proportion with each staging of disease	I-II: 79.0% III-IV: 21.0% Source: Gupta 2021.	DUSC considered that a proportion of Stage III patients would be treated with curative intent and should be added to the estimate of the number of Stage I and II patients.
Proportion with Stage I-II first recurrence	Recurrence rate: 7.2% Source: Francis 2019.	May be underestimated. A higher recurrence rate (13% and 12.4%) was reported by Fung-Kee-Fung 2006 and Huijgens 2013 respectively. It may be more appropriate to estimate different rates of recurrence for de novo Stage I, II and III patients treated with curative intent and patients with unresectable Stage III and IV treated with palliative intent chemotherapy. DUSC considered that most patients will recur early.
Proportion receiving 1L PBC (pre and post - introduction of dostarlimab)	72% (90% eligible for 1L treatment; 80% of whom treated with PBC) Source: Australian clinical expert opinion (n=5) provided during the Advisory Board in 2021. The proportion receiving 1L PBC was implicitly assumed to be 72% by the submission both before and after introduction of dostarlimab.	Survey results were based on five anonymous respondents and may be uncertain. The proportion of patients treated with PBC could not be verified during evaluation. The proportion receiving 1L PBC post-introduction of dostarlimab was likely underestimated as usage of 1L PBC will likely increase post dostarlimab listing as it would be a requirement for access. DUSC considered that: <ul style="list-style-type: none"> • A larger proportion of Stage III and IV patients would receive 1L PBC in the adjuvant or advanced setting, and 72% was an underestimate in this group. • High risk Stage I and II patients who are more likely to relapse would receive 1L platinum chemotherapy, and 72% was an underestimate in this group. • A small minority of Stage I and II patients with loco-regional recurrence (for example, vaginal) would be likely to be treated with salvage radiotherapy or surgery and may not receive PBC, and 72% was an overestimate in this small group.
Proportion who progress following 1L PBC	The probability of progression following 1L PBC followed a typical pattern (observed to be highest in Yr 2 and 3, followed by slower rate of progression over the later years). Source: Miller 2020.	The proportion of patients who progressed following 1L PBC were likely underestimated. Progression was applied inconsistently (2027 estimates had 10 years' worth of progression, while estimates for 2022 were limited to six years of progression). It was unclear why a maximum of 10 years was used by the submission even though data up to 14 years were available.

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Data	Value and Source	Comment
Proportion with ECOG 0-1	80% Source: Australian clinical expert opinion (n=5) provided during the Advisory Board in 2021.	DUSC considered that 80% was overestimated and that 70% may be a more reasonable estimate.
Proportion with dMMR	33% Source: Scarpa 2016.	DUSC considered this may be overestimated, 27% (based on Gupta 2021) may be a more reasonable estimate.
Treatment utilisation		
Uptake rate	█% Source: Australian clinical expert opinion (n=5) provided during the Advisory Board in 2021. The submission noted that █% of these patients would have otherwise been treated with standard chemotherapy regimens and the remaining portion of patients (█%) would have otherwise received best supportive care.	DUSC considered this appeared to be reasonable.
Proportional utilisation among nominated basket of chemotherapies	Doxorubicin: 36% Paclitaxel: 52% Carboplatin: 68% Source: UK RWE study and verified by clinical expert opinion.	The evaluation considered the UK study may not be applicable to the Australian setting and was inconsistent with the nominated comparator (100% doxorubicin) in the submission's economic model. The total usage exceeded 100%, suggesting that some patients will use combination therapies. DUSC considered this input could be reasonable.
Mean duration of treatment*	Dostarlimab: 54.37 weeks (revised in the PSCR without half cycle correction) Source: Economic model – GARNET Cohort A1 study. SoC: 12.75 weeks Source: UK RWE study.	Duration of SoC was reasonable but not consistent with base case of economic model which assumed 12 weeks (4 cycles) based on ZoptEC.
Costs		
Infusion costs	\$112.40 (MBS rebate rate of 80% used) applied per script per patient. Source: MBS item 13950, parenteral administration of one or more antineoplastic agents.	Appropriate.
Adverse events	Cost of managing adverse events not included.	DUSC considered the AE profile of dostarlimab is different from chemotherapy and should be accounted for in the financial estimates.

Source: Table 122&123, p213&217 of the submission.

1L = first-line; AIHW = Australian Institute of Health and Welfare; dMMR = mismatch repair deficient; ECOG = Eastern Cooperative Oncology Group; MBS = Medicare Benefits Schedule; NZ = New Zealand; PBC = platinum-based chemotherapy.

* 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.

6.73 The estimated financial impact of PBS listing dostarlimab is summarised in Table 15.

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Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patients treated with dostarlimab (█ %)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts						
Initiating scripts ^a	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Continuing scripts ^b	█ ¹	█ ¹	█ ²	█ ²	█ ²	█ ²
Total	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
PBS/RPBS cost less co-pay						
Total (eff) – submission (\$)	█ ³	█ ³	█ ³	█ ³	█ ⁴	█ ⁴
Total (eff) ^d – PSCR (\$)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Total (eff) ^e pre-PBAC response (\$)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Changes in number of scripts (carboplatin; doxorubicin; paclitaxel)						
Total	█ ⁻¹	█ ⁻¹	█ ⁻¹	█ ⁻¹	█ ⁻¹	█ ⁻²
PBS/RPBS cost less co-pay (DPMA) ^c (carboplatin; doxorubicin; paclitaxel)						
Total (pub/eff) ^e (\$)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to PBS/RPBS (eff) ^e (\$)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net MBS costs (\$)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to PBS/RPBS/MBS submission (\$)	█ ³	█ ³	█ ³	█ ³	█ ⁴	█ ⁴
Net cost to PBS/RPBS/MBS ^d – PSCR (\$)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to PBS/RPBS/MBS ^e pre-PBAC response (\$)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³

Source: Tables 123,125,127,128,131-134,137,140,141,143,144,146,148,149, pp 217,219, 221-223, 225, 228-233 of the submission.

DPMA = dispensed price maximum amount; eff = effective; MBS = Medicare Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; pub = published; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a number of patients × █ scripts for each initiation

^b number of patients × █ scripts (based on 50.97 weeks minus 12 weeks divided by 6 weekly doses)

^c An error was identified during the evaluation where co-payment was calculated by the submission by dividing by the number of maximum scripts. This was incorrect given under the efficient funding of chemotherapy, patients only make one co-payment per original script, and slightly underestimated the costs offsets of chemotherapy. Values were rectified during the evaluation.

^d Updated in the Pre-Sub-Committee Response (Excel file 'Jemperli (dostarlimab) 2L dMMR EC BIM_PSCR.xlsx')

^e Updated in the pre-PBAC response (Excel file 'Jemperli (dostarlimab) 2L dMMR EC BIM_Pre-PBAC.xlsx')

The redacted values correspond to the following ranges:

1 <500

2 500 <5,000

3 \$0 to <\$10 million

4 \$10 million to <\$20 million

6.74 The estimated net cost to PBS/RPBS/MBS at the submission’s proposed effective price was \$0 to < \$10 million in Year 1, increasing to \$10 million to < \$20 million in Year 6. The total cost over the six year period was estimated to be \$50 million to < \$60 million. This was reduced to \$30 million to < \$40 million over 6 years in the PSCR due to the reduced proposed price for dostarlimab.

6.75 Overall, the evaluation considered that the financial estimates were likely underestimated by the submission as the usage of dostarlimab would have been underestimated due to the following:

- The treatment duration assumed (50.97 weeks) was incorrectly calculated. This was revised to 54.37 weeks in the PSCR;
- The recurrence rate (7.2%) used by the submission may be underestimated given two sources (Fung-Kee-Fung 2006 and Huijgens 2013) indicated this was higher (13% and 12.4% respectively);

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- The submission assumed that treatment patterns of 1L therapy would remain the same pre- and post-introduction of dostarlimab. However, the availability of dostarlimab as 2L treatment (and the high uptake rate anticipated by the submission) may alter usage patterns of 1L PBC given this would be a requirement. More patients using 1L PBC would lead to a higher proportion of eligible patients than the 72% of all A/R dMMR EC patients assumed;
- Progression after 1L PBC was inconsistently applied by the submission using a period of up to 10 years post treatment, even though data up to 14 years were available. Using fewer years of data would underestimate number of recurrent patients; and
- There was no consideration of patients who may use dostarlimab as third (or subsequent) line therapy (i.e. among the 28% who did not receive 1L PBC, but who may subsequently receive 2L PBC). Omission of these patients may underestimate the financial estimates.

6.76 DUSC also considered the estimates presented in the submission to be underestimated. The main issues identified by DUSC were:

- Prevalent patients (those diagnosed prior to year 1 of the estimates who recur and become eligible for dostarlimab) should be added to the financial estimates, which will increase the number of treated patients in years 1 and 2 of the estimates.
- Stage III patients should not be grouped together with Stage IV patients. More appropriate treated population groups would be:
 - Resectable high risk Stage I, II and III patients treated with curative intent (surgery) with adjuvant radiation therapy platinum chemotherapy, some of which would recur, be classified as recurrent disease and would be eligible for dostarlimab.
 - Unresectable Stage III and IV patients treated with palliative intent chemotherapy, almost all of which would progress and be eligible for dostarlimab.
- The proportion of patients with dMMR (33%) may be overestimated, and 27% may be a more reasonable estimate.
- The financial estimates presented by the submission were likely underestimated, as the treatment duration and the number of patients treated with dostarlimab were both likely underestimated. However, given that the proposed RSA was to be based on the values presented in the submission, an underestimation of the financial estimates may be considered conservative.

6.77 The pre-PBAC response stated that “Stage I/II patients who recur and become eligible for dostarlimab in year 1 to 6 (2022-2027) were derived from a prevalent pool of Stage I/II patients diagnosed from 2016 onwards (prior to year 1) and adjusted for timing as disease recurrence was expected to occur over time. As such, the financial estimates have implicitly accounted for those diagnosed prior to year 1”. The pre-PBAC response

also provided revised estimates (as shown in Table 15) incorporating the following changes:

- A recurrence rate of 13%
- 81% of Stage III/IV patients receiving 1L PBC
- dMMR prevalence rate of 27%
- Revised effective price (\$)

Following these changes, the estimated net cost to PBS/RPBS/MBS at the pre-PBAC response's revised effective price was \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6. The total cost over the six year period was estimated to be \$30 million to < \$40 million.

Quality use of Medicines

- 6.78 The submission 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 Arrangement

- 6.79 The submission indicated that the sponsor was willing to consider a risk sharing arrangement according to the base case financial estimates but did not provide further details.

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 that 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. Overall, the PBAC considered that the magnitude of benefit for dostarlimab over chemotherapy was uncertain and the incremental cost-effectiveness ratio was highly uncertain because the modelled survival benefit was not adequately supported by the available data.
- 7.2 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.

- 7.3 The PBAC considered that the submission's proposed clinical place for dostarlimab, which was in patients with dMMR EC who have progressed on or following prior treatment with a platinum-based chemotherapy (PBC), was appropriate in line with the available evidence from the GARNET study. The PBAC noted there was an on-going randomised, double-blind phase III study of dostarlimab in combination with 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.
- 7.4 The submission nominated SoC comprising single-agent chemotherapy and PBC as the main comparator. The PBAC noted that some patients would be expected to receive combination chemotherapy (e.g. carboplatin + paclitaxel or doxorubicin). 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.
- 7.5 The PBAC noted that the evidence for dostarlimab was based on a cohort of patients with dMMR/MSI-H endometrial cancer from an on-going, single-arm, open-label, phase I/II study of dostarlimab in patients with advanced solid tumours (the GARNET study). The submission presented: naïve indirect comparisons of GARNET Cohort A1 (n=129 in the submission data-cut IA-2) versus the SoC arms of four randomised trials and one descriptive, non-interventional cohort study (UK RWE); and an IPTW analysis comparing dostarlimab to doxorubicin. The PBAC noted that even with the longer follow-up provided in the PSCR, the OS data from GARNET Cohort A1 were relatively immature with median survival not reached. The PBAC considered 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.
- 7.6 From the naïve comparison, the lower confidence limit for median OS of 27.1 months was higher than the upper confidence limit on SoC arms in the included studies (11.1-19.6 months, including the UK RWE). The PBAC noted the submission reported a statistically significant improvement in OS for dostarlimab versus doxorubicin, based on the IPTW comparison (HR=0.41; 95% CI: 0.28, 0.61; p<0.0001), which was consistent with the naïve indirect comparisons. However, the PBAC noted that only a small benefit in PFS was observed in the indirect naïve comparison, which did not meet the MCID. The PBAC considered that dostarlimab appears to demonstrate clinical activity in dMMR EC, however the magnitude of benefit in terms of OS and PFS is uncertain due to the low quality evidence, the immaturity of the data, and limitations of the indirect comparisons.
- 7.7 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. The PBAC noted that Grade ≥ 3 TEAEs and treatment related Grade ≥ 3 TEAEs were generally slightly lower in GARNET Cohort A1 than in the SoC studies. Noting the limitations of the safety data available for dostarlimab, the PBAC 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.

- 7.8 The PBAC noted that the PSCR provided a comparison with pembrolizumab \pm lenvatinib. The PBAC noted that comparison was a naïve indirect comparison based on the single arm dostarlimab study and the KEYNOTE-158 and KEYNOTE-775 trials for pembrolizumab \pm lenvatinib. The PBAC considered that a comparison with pembrolizumab \pm lenvatinib, to support a claim of non-inferior effectiveness, would require full independent evaluation.
- 7.9 The submission presented a stepped economic evaluation of dostarlimab versus SoC in A/R dMMR EC following PBC based on the GARNET Cohort A1 (dostarlimab) and ZoptEC (doxorubicin). The PBAC noted that, when different parametric survival curves were fitted to the Kaplan-Meier data for dostarlimab (using the GARNET Cohort A1, IA-2 data-cut), there was a large variance in extrapolations of OS, which was more pronounced with longer extrapolations. The PBAC noted that the extrapolation method resulted in the model estimating a large incremental difference in survival with dostarlimab versus SoC over the course of the model time horizon (even with a 6.25 year time horizon, as proposed in the pre-PBAC response). The PBAC considered that the choice of the parametric extrapolation function, based on an assumed plateau of OS was not well supported by the GARNET data, as the results were relatively immature, and this was a major source of uncertainty in the assessment of cost-effectiveness.
- 7.10 The PBAC noted that the pre-PBAC response attempted to address the uncertainty associated with the long-term survival estimates by providing a revised model including survival curve convergence (between 5 and 7.5 years) and removal of terminal care costs and an alternative analysis (which resulted in a similar ICER/QALY but did not require structural changes to the evaluated model) with a 6.25 year time horizon (no convergence) and removal of terminal care costs. The PBAC noted that the requested price for dostarlimab was reduced to maintain an ICER of \$55,000 to $<$ \$75,000/QALY. The PBAC considered that the ICER remained highly uncertain due to the uncertain magnitude of benefit for dostarlimab, based on data from a relatively small single arm study. The PBAC considered that the ICER was unacceptably high given the level of uncertainty in the magnitude of benefit and long-term OS.
- 7.11 The PBAC considered that the submission's financial estimates appeared underestimated due to: an underestimated recurrence rate; assumptions regarding 1L treatment patterns remaining unchanged; assumptions regarding progression after 1L PBC being applied inconsistently; and exclusion of patients who may use

dostarlimab as third (or subsequent) line therapy. However, the proportion of patients with dMMR appeared to be overestimated. The PBAC noted that the pre-PBAC response provided revised financial estimates incorporating the following changes: a recurrence rate of 13%, 81% of Stage III/IV patients receiving 1L PBC, dMMR prevalence rate of 27% and the revised effective price. The PBAC considered these changes were appropriate and given that the submission's proposed RSA was to be based on the financial estimates presented in the submission, any underestimation of the financial estimates may be considered conservative.

- 7.12 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. The PBAC considered that a comparison with pembrolizumab ± lenvatinib would require a full analysis as per the PBAC guidelines and evaluation. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway. Alternatively, the PBAC considered that data from the RUBY trial may support an alternative clinical place for dostarlimab in earlier line EC in combination with chemotherapy.
- 7.13 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

GSK is disappointed by the PBAC's decision not to recommend dostarlimab (Jemperli®) for the treatment of patients with recurrent or advanced mismatch repair deficient endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen. However, we remain committed to working with the PBAC to ensure Australian women with endometrial cancer have timely access to Jemperli®.