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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]

Appraisal Committee Meeting – 2 November 2021
1st Committee meeting

The following documents are made available to the Company:

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission summary** from GlaxoSmithKline

2. **Clarification questions and company responses**
   2a. Clarification questions
   2b. Company responses

3. **Patient group, professional group and NHS organisation submissions** from:
   a. NCRI-ACP-RCP-RCR

4. **Evidence Review Group report** prepared by Warwick Evidence

5. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Dr Susana Banerjee, Consultant Medical Oncologist – clinical expert, nominated by GSK (company)
   b. Andrew Clamp, Consultant and Honorary Senior Lecturer in Medical Oncology – clinical expert, nominated by GSK (company)
   c. Hilary Maxwell, Gynae-Oncology Clinical Nurse Specialist – patient expert, nominated by Go Girls

8. **Evidence Review Group critique of company response to technical engagement** prepared by Warwick Evidence

9. **Appraisal Committee Meeting presentation slides** (uploaded separately)

Please note that the full submission, appendices to the company's submission and

company model will be available as a separate file on NICE Docs for information only.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dostarlimab for previously treated advanced and recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]

Document B

Company evidence submission

17 May 2021

File name	Version	Contains confidential information	Date
Document B	FINAL	Yes	17th May 2021

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

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Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

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Abbreviations

AE	Adverse event
AUC	Arena under the curve
BGCS	British Gynaecological Cancer Society
BICR	Blinded independent central review
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
BSC	Best standard of care
CASP	Critical Appraisal Skills Programme
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle X Day X
DCO	Data cut off
DCR	Disease control rate
DG	Diagnostics guidance
dMMR	DNA mismatch repair deficient
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision support unit
EC	Endometrial cancer
ECOG PS	Eastern Cooperative Oncology Group performance score
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EORTC QLQ-C3-	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	End-of-treatment
EQ-5D	EuroQoL 5-dimensions 5-levels
ESGO	European Society of Gynecological Oncology
ESMO	European Society for Medical Oncology Annual Meeting
ESP	European Society of Pathology
ESS	Effective sample size
ESTRO	European Society for Radiotherapy and Oncology
FIGO	International Federation of Gynaecology and Obstetrics
HR	Hazard ratio
HR+	Hormone receptor positive
HRQoL	Health-related quality of life
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
I-O	Immuno-oncology
IPD	Individual patient data
IPTW	Inverse probability treatment weighting
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan-Meier
LYG	Life-years gained
MAIC	Matching-adjusted indirect comparison

MHRA	Medicines & Healthcare products Regulatory Agency
MSI-H	Microsatellite instability-high
MSS	Microsatellite stable
NCRAS	National Cancer Registry Analysis System
NHS(E)	National Health Service (England)
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PD-L1/2	Programmed death-ligand 1/2
PFS	Progression-free survival
PH	Proportional hazards
PLD	Pegylated liposomal doxorubicin
pMMR	DNA mismatch repair proficient
PPS	Post-progression survival
PR	Partial response
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QXW	Once every X weeks
QALY	Quality-adjusted life-years
QOL	Quality of life
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
RWE	Real-world evidence
SACT	Systemic Anti-Cancer Therapy (SACT) dataset
SAE	Serious adverse event
SD	Stable disease
SLR	Systematic literature review
STC	Simulated treatment comparisons
STD	Standard deviation
TEAE	Treatment emergent adverse event
TTNT	Time to next treatment
ToT	Time on treatment
TTD	Time to discontinuation
TTNT	Time to next treatment
VAS	Visual analogue scale

B.1 Decision problem, description of the technology and clinical care pathway

Recurrent or advanced dMMR/MSI-H EC

- Dostarlimab is a treatment for patients with recurrent or advanced DNA mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.[1]
- This patient population, which equates to approximately 124 women each year in England (see Section B.1.3.3), reflects a small, well-defined proportion of the total EC population, and represents those with the greatest critical unmet need.
- Once patients are diagnosed with recurrent or advanced EC, they face an extremely poor prognosis; only 15% and 20% of patients diagnosed with advanced EC and recurrent EC, respectively, will survive for longer than five years.[2-5]
- First line platinum-based chemotherapy is the mainstay of initial treatment for patients with recurrent or advanced EC, but regrettably, disease progression is inevitable and only one in every three patients will ever receive another line of treatment – the remaining patients will have died or be too unwell to withstand further treatment. Following progression on or after platinum-based chemotherapy, patients face a bleak prognosis with no recognised standard of care treatments and a median overall survival (OS) of less than one year.[6-11]

Current clinical pathway of care

- With no standard of care treatments available following disease progression on platinum-based chemotherapy, patients in this setting are left with extremely limited and inadequate treatment options, based on unclear and inconsistent treatment guidelines.
- Many patients will receive further lines of chemotherapy but by this stage, EC is largely considered to be a chemotherapy-resistant disease.[12] Real-world evidence (RWE) in the UK shows that patients receiving further chemotherapy face a median OS of just [redacted] months (95% CI: [redacted], [redacted]).[13] Only [redacted]% (95% CI: [redacted], [redacted]) and [redacted]% (95% CI: [redacted], [redacted]) of patients were alive after one and two years, respectively.[13] A small number of patients may alternatively receive hormone therapy, despite the lack of published evidence that it provides any benefit in this setting.[14]
- The lack of effective treatment options has a detrimental psychological impact on patients, leaving them feeling underserved and abandoned. The critical unmet need for a more effective treatment is so severe that unlicensed nivolumab monotherapy is temporarily available via the Cancer Drugs Fund (CDF) through a COVID-19 response programme, despite there being no clinical evidence to support its use in this patient population.[15]

Dostarlimab

- Dostarlimab is a novel and innovative immuno-oncology (I-O) therapy that represents a significant step-change for patients with recurrent or advanced dMMR/MSI-H EC tht has progressed on or after a platinum-containing regimen.
- In the single-arm pivotal GARNET trial (see Section B.2.3.1); interim analysis data when compared with RWE on current clinical management shows that dostarlimab potentially improves survival for this patient group. Overall [redacted]% (95% CI: [redacted], [redacted]) of patients treated with dostarlimab were alive after one year, and [redacted]% of patients were still alive after two years, [redacted] the proportion of patients alive at two years in current UK clinical practice based on RWE.[13, 16]
- Dostarlimab represents a critical addition to the treatment armamentarium for patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or after a platinum-containing regimen, who will otherwise continue to face an extremely bleak prognosis with a limited life expectancy and almost no hope of receiving effective treatment.

B.1.1 Decision problem

This submission demonstrates the clinical and cost-effectiveness of dostarlimab within its full marketing authorisation as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.

The decision problem addressed within this submission is broadly consistent with the NICE final scope for this appraisal as outlined in Table 1. The principal difference relates to the comparators considered relevant to this appraisal as detailed in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously treated advanced or recurrent EC with MSI-H or dMMR.	Patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or following prior treatment with a platinum-containing regimen.	The patient population is aligned with the NICE final scope, though it is important to note that patients eligible for dostarlimab must *have progressed on or following prior treatment with a platinum-containing regimen.* This is in line with the marketing authorisation for dostarlimab in this indication and the patient population included in the pivotal GARNET trial (see Section B.2.3.1).
Intervention	Dostarlimab	Dostarlimab	NA – aligned with the NICE final scope.
Comparator(s)	• Chemotherapy, including: ○ Carboplatin and paclitaxel ○ Paclitaxel monotherapy ○ Doxorubicin monotherapy ○ Carboplatin monotherapy • Hormone therapy (such as medroxyprogesterone acetate and megestrol) • Best supportive care (BSC)	**Base case cost-effectiveness analysis:** • A basket of treatments representing current clinical management, comprising: ○ Carboplatin plus paclitaxel ○ Paclitaxel monotherapy ○ Carboplatin plus pegylated liposomal doxorubicin (PLD) ○ PLD monotherapy ○ Carboplatin monotherapy ○ Hormone therapy (50:50 ratio of medroxyprogesterone and letrozole)	**Current clinical management** • In the absence of a definitive standard of care or clear treatment guidelines for this indication, the base case cost-effectiveness analysis compares dostarlimab to current clinical management in the UK as a basket of comparator therapies. This consists of aggregate data for patients receiving a range of the most commonly prescribed chemotherapy regimens in patients with recurrent or advanced EC who have progressed on or after a platinum-containing regimen in clinical practice, based on a GSK-initiated real-world evidence (RWE) study using data from the National Cancer Registry Analysis System (NCRAS) in England (hereafter referred to as the UK RWE study).

		Scenario analyses:
		• Individual comparisons versus:
		  ○ Carboplatin plus paclitaxel
		  ○ Paclitaxel monotherapy
		  ○ Doxorubicin monotherapy
		  ○ Carboplatin monotherapy
		  ○ Hormone therapy (50:50 ratio of medroxyprogesterone and letrozole)
			• The treatments included in this aggregate data include the individual chemotherapy regimens listed in the final scope, as well as carboplatin plus PLD. As the UK RWE study could not capture hormone therapy, the costs of hormone therapy (a weighted average of medroxyprogesterone acetate and letrozole based on UK clinical expert feedback) have instead been incorporated within the basket.
			• An SLR was conducted to identify relevant clinical evidence for the individual therapies listed in the NICE final scope however these data were extremely limited; most studies in the relevant patient population were observational studies, where patient characteristics and Kaplan-Meier (KM) survival data were poorly reported. Where possible, scenario analyses have been conducted versus the comparators for which data were identified in the literature in the post-platinum chemotherapy setting.
			• No data were identified for either carboplatin monotherapy or hormone therapy. Despite efforts made to identify alternative sources of data for these comparators, feedback from UK clinical experts strongly indicated that any data for patients not in the post-platinum chemotherapy setting would not be suitable to use as a proxy for these comparators. The UK clinical experts also indicated that survival with hormone therapy or carboplatin monotherapy would not be expected to exceed that observed in the UK RWE study. As such, individual comparisons have been explored between dostarlimab and carboplatin monotherapy and hormone therapy in scenario analyses, using efficacy data for doxorubicin monotherapy and current clinical management as a proxy, respectively (See Section B.3.8.3).
			Removal of BSC
			• BSC was not fully defined in the NICE final scope, and there is a lack of standardised definition in the literature.

			It is likely to consist of pain and symptom management or relief with treatment such as analgesics and corticosteroids. • BSC is not considered a relevant comparator to dostarlimab in this submission and a comparison versus BSC has not been included, for the following reasons: ○ Feedback from UK clinical experts is that, for most patients, BSC would be used as an add-on therapy to chemotherapy and thus is expected to be used as an add-on therapy to dostarlimab.[16] Accordingly, UK clinical experts agreed that BSC would not represent a relevant comparator to dostarlimab.[16] ○ Whilst a small proportion of patients with recurrent or advanced EC who have progressed on or after a platinum-containing regimen may receive palliative therapy as BSC, these patients reflect a different patient population (of more severely unwell patients) compared to the proposed target population for dostarlimab.
Outcomes	• Progression-free survival • Overall survival • Response rates • Duration of response • Adverse effects of treatment • Health-related quality of life	• Progression-free survival • Overall survival • Response rates (overall response rates, disease control rate) • Duration of response • Adverse effects of treatment • Health-related quality of life	NA – aligned with the NICE final scope.
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • The reference case stipulates that the time	• An economic analysis has been conducted with the cost-effectiveness of treatments expressed in terms of incremental cost per quality-adjusted life year. • A lifetime time horizon has been adopted to reflect all differences in costs and outcomes between the	• Regarding the costs associated with diagnostic testing, NICE diagnostics guidance DG42 recommends that all patients with EC should be tested using immunohistochemistry (IHC) to identify tumours with dMMR/MSI-H.[18] DG42 recommends that IHC testing for dMMR is the preferred approach, and clinical expert opinion sought by GSK agreed with this.[16] Additionally, discussions with NHSE at a surgery confirmed that

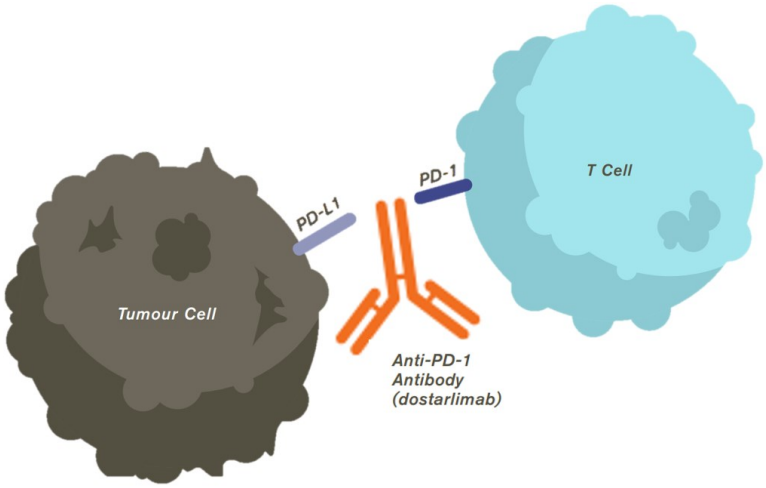
	horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. • The economic modelling should include the costs associated with diagnostic testing for microsatellite instability status in people with endometrial cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.[17]	technologies being compared. • Costs are considered from an NHS and Personal Social Services perspective. • A confidential commercial discount to the list price of dostarlimab has been adopted within the base case analysis. • Any commercial arrangements for the comparators are not known and have therefore not been taken into account. • The inclusion of diagnostic testing for dMMR/MSI-H status has been explored within a scenario analysis, which considers dMMR/MSI-H testing for recurrent patients only (see Section B.3.8.3).	testing would not be an issue for access to dostarlimab. • Furthermore, given the availability of nivolumab through the Cancer Drugs Fund (CDF) for patients with dMMR/MSI-H, dMMR testing is already in use in clinical practice to identify eligible patients, and therefore resources for dMMR testing are already being embedded within usual practice. • As such, dMMR testing will soon become standard of care for all patients with EC and no additional diagnostic tests will be required to facilitate the prescribing of dostarlimab beyond those already conducted for patients with EC in UK NHS clinical practice. These costs have therefore not been included within the base case economic analysis, but a scenario analysis has been conducted to explore the impact of the inclusion of diagnostic testing costs for dMMR status for recurrent patients only.

Abbreviations: BSC: best supportive care; CDF: Cancer Drugs Fund; DG: diagnostics guidance; dMMR: DNA mismatch repair deficiency; EC: endometrial cancer; GSK: GlaxoSmithKline; IHC: immunohistochemistry; KM: Kaplan-Meier; MSI-H: microsatellite instability-high; NA: not applicable; NCRAS: National Cancer Registry Analysis System; NHS(E): National Health Service (England); NICE: National Institute for Health and Care Excellence; PLD: pegylated liposomal doxorubicin; RWE: real-world evidence.

B.1.2 Description of the technology being appraised

A description of the technology being appraised (dostarlimab [Jemperli]®) is provided in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Dostarlimab (Jemperli®)
Mechanism of action	Dostarlimab is a humanised, monoclonal antibody which binds with high affinity and specificity to programmed cell death protein 1 (PD-1), a cell surface receptor expressed on activated T-cells.[19] PD-1 and its two known ligands, programmed cell death ligands 1/2 (PD-L1 and PD-L2), are part of a complex signalling system which controls T-cell activation. The PD-1/PD-L1 checkpoint serves as a negative regulator of T-cells, which typically helps to control local inflammatory responses. PD-L1 is constitutively expressed on a subset of macrophages, but it can also be expressed on tumour cells.[20] In the tumour microenvironment, PD-L1 expressed on the surface of tumour cells binds to PD-1 on activated T-cells in a process called immune evasion.[21] This results in T-cell inhibition, suppressing subsequent cytokine production and cytotoxicity. This dampening of the immune response prevents T-cells from killing the tumour cells, enabling the tumour to continue to grow without restriction.[21, 22] By inhibiting the binding of PD-1 to PD-L1 and PD-L2, dostarlimab blocks the PD-1 signalling pathway and subsequent immune evasion resulting in an increased anti-tumour immune response and cancer cell death (Figure 1). **Figure 1: Mechanism of action of dostarlimab binding with PD-1 receptor**  **Source:** GSK Infographic. **dMMR/MSI-H EC** DNA mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer (EC), is a subtype of EC that comprises approximately 23% of all EC cases (see Section B.1.3.2) and represents

	a subgroup where PD-1/PD-L1 inhibition with I-O therapy is most effective.[18, 23] dMMR/MSI-H EC is highly immunogenic, and exhibits more tumour-specific neoantigens, which results in increased T-cells, including tumour-infiltrating lymphocytes, and compensatory upregulation of immune checkpoints.[23] This combination of increased mutation load, T-cells and PD-1/PD-L1 expression means that dMMR/MSI-H EC represents an ideal target for dostarlimab and PD-1/PD-L1 inhibition.[23]
Marketing authorisation/CE mark status	A regulatory submission for dostarlimab as a new active substance has been made via the European Medicines Agency (EMA) centralised procedure. Committee for Medicinal Products for Human Use (CHMP) positive opinion was received on 25th February 2021, recommending the granting of conditional marketing authorisation. A conditional marketing authorisation is granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the limitation inherent in the fact that additional data are still required. It is issued with the expectation that comprehensive clinical data is provided at a later stage. EMA regulatory approval was received on 21st April 2021. An application to the Medicines and Healthcare Regulatory Agency (MHRA) for a UK marketing authorisation has also been made for dostarlimab via the European Commission Decision Reliance Procedure (ECDRP), for the MHRA to adopt the CHMP opinion and thus convert to a national licence.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	"Jemperli is indicated as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum containing regimen."[1]
Method of administration and dosage	Dostarlimab 500 mg is administered via a 30-minute IV infusion every 3 weeks (Q3W) (Day 1 of each 21-day cycle) for the first 4 cycles.[1] This is followed by dostarlimab 1,000 mg administered via IV infusion every 6 weeks (Q6W) (Day 1 of each 42-day cycle) for all subsequent cycles.[1]
Additional tests or investigations	NICE diagnostics guidance DG42 recommends that all patients with EC should be tested to identify tumours with dMMR/MSI-H.[18] DG42 recommends that testing for dMMR/MSI-H tumours should consist of dMMR testing via immunohistochemistry (IHC), and clinical expert opinion sought by GSK for this submission agreed that this would be the preferred testing approach and that all patients eligible for treatment with dostarlimab would receive dMMR testing as a result of this guidance.[16] Consultation with NHS England (NHSE) via an NHSE surgery also confirmed the availability of dMMR testing across England, and that access to testing will not be a barrier to accessing dostarlimab upon reimbursement. Consequently, dMMR testing via IHC will soon become standard of care for all patients with EC, and no additional diagnostic tests will be required to facilitate the prescribing of dostarlimab beyond those already conducted for patients with EC in UK NHS clinical practice.

List price and average cost of a course of treatment	The list price of dostarlimab is £[redacted] per 500 mg vial. Based on the time on treatment in the base case cost-effectiveness analysis, the average discounted cost per course of treatment with dostarlimab (including drug acquisition and administration costs) is [redacted] at list price and [redacted] when including the patient access scheme (PAS) discount for dostarlimab (see below).
Patient access scheme (if applicable)	A confidential simple PAS discount application has been submitted by GSK that provides dostarlimab at a net price of £[redacted] per 500 mg vial.

Abbreviations: CHMP: Committee for Medicinal Products for Human Use; dMMR: DNA mismatch repair deficiency; DG: diagnostics guidance; EC: endometrial cancer; ECDRP: European Commission Decision Reliance Procedure; EMA: European Medicines Agency; GSK: GlaxoSmithKline; IHC: immunohistochemistry; IV: intravenous; MHRA: Medicines and Healthcare Regulatory Agency; MSI-H: microsatellite instability-high; NA: not applicable; NHS(E): National Health Service (England); PAS: patient access scheme; PD-1/2: programmed cell death protein 1/2; PDL-1/2: programmed cell death-ligand 1/2; QXW: once every X weeks; SmPC: Summary of Product Characteristics.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Overview of endometrial cancer

EC is a type of uterine cancer that originates in the lining of the womb (uterus), known as the endometrium. The term EC is frequently used synonymously with uterine cancer, since a large majority (~94%) of uterine cancers are EC.[24] However, other types of uterine cancer are clinically distinct and are treated differently to EC.[25]

EC contributes to an estimated 2,162 deaths every year in the UK, with an age-adjusted mortality rate (the number of deaths due to EC occurring in a specified population over a given period of time) of 2.6 per 100,000 patients in 2018.[26, 27] In the UK, EC is responsible for approximately one woman's death every four hours.[24, 26]

This submission focusses on patients with recurrent or advanced dMMR/MSI-H EC (see Section B.1.3.2) who have progressed on or following prior treatment with a platinum-containing regimen. This patient population, which equates to approximately 124 patients each year in England, focusses on a small, well-defined proportion of the total EC population, and reflects the population of patients with the greatest critical unmet need.

Patients with recurrent or advanced EC face an extremely poor prognosis – only 15% of patients diagnosed with advanced (Stage IV) disease will survive longer than five years, compared to 92.2% of patients with Stage I disease.[2] Fewer than half (46.5%) of patients with Stage IV EC will survive for more than one year.[14, 28] Similarly, only 20% of patients who experience disease recurrence from earlier stages of disease will survive for five years, versus 89% of patients without disease recurrence.[3-5] Advanced EC is also associated with a range of debilitating symptoms, deteriorations in physical functioning and health-related quality of life (HRQoL).[29-31]

For patients with recurrent or advanced EC, first-line platinum-based chemotherapy is the standard of care, and is currently their last chance to receive effective treatment. Regrettably, most patients will progress past this first line of therapy, and feedback from UK clinical experts is

that only one in every three patients will ever receive another line of treatment – the remaining patients will have died or be too unwell to withstand further treatment.[16]

Disease progression carries devastating and distressing consequences and an extremely bleak prognosis. No evidence based standard of care treatments are available in the post-platinum chemotherapy or subsequent settings, leaving patients with extremely limited and inadequate treatment options based on unclear and inconsistent treatment guidelines. The lack of subsequent effective treatment options has a detrimental psychological impact on patients, leaving them feeling underserved and abandoned.

Most patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or following prior treatment with a platinum-containing regimen will go on to receive further lines of chemotherapy, either as monotherapy or as a doublet chemotherapy regimen. However, each subsequent line of chemotherapy results in increased chemoresistance and is associated with a substantial burden of toxicity.[12, 16] Data from a GSK-initiated UK RWE study show that further chemotherapy in this setting is associated with a median OS of just [redacted] months (95% CI: [redacted], [redacted]), with only [redacted]% and [redacted]% of patients alive after one and two years, respectively (see Section B.2.3.2).[13]

Alternatively, some patients who have high oestrogen or progesterone receptor expression in the tumour (known as hormone receptor positive [HR+]) may receive hormone therapy, such as letrozole or medroxyprogesterone acetate, despite no evidence that it provides any survival benefit in this post-platinum setting.[14] This highlights the significant unmet need clinically, that when faced with extremely limited treatment options, clinicians are willing to administer non-evidence based treatments in the hope that they will provide some benefit for patients in this setting.

Patients with recurrent or advanced EC who progress on or after platinum-based chemotherapy unequivocally deserve an effective, evidence-based treatment option. This critical unmet need is so severe that currently unlicensed nivolumab is available via the Cancer Drugs Fund (CDF) for patients with metastatic or locally advanced dMMR/MSI-H EC through a COVID-19 response programme, despite there being no available clinical evidence in support of its use in this patient population.[15]

B.1.3.2 Disease classification, progression and recurrence

Dostarlimab is a treatment option for adult patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or following prior treatment with a platinum-based chemotherapy regimen, in line with its marketing authorisation.

It is important to note that, whilst patients with recurrent EC and patients with advanced EC may have different treatment histories, they are viewed as one patient population in clinical practice following the treatment of recurrent or advanced EC with platinum-based chemotherapy. As such, patients with recurrent EC and patients with advanced EC in the post-platinum chemotherapy setting are viewed together as one within this appraisal. This population represents the patients that face the worst prognosis, and those with a critical unmet need.

Advanced disease

Upon diagnosis, EC is staged according to the International Federation of Gynaecology and Obstetrics (FIGO) system.[32] FIGO Stages I–II are considered early stage EC, at which point the

disease has not spread outside of the uterus. The majority of patients with EC (approximately 80%) are diagnosed at an early stage (Table 3).[33]

A smaller number of EC patients (15–20%) will be diagnosed with advanced stage cancer (Stage III and IV), at which point the disease has spread beyond the uterus (Table 3).[33] Patients with advanced stages (Stage III and IV) of disease, have a much poorer prognosis. Only 50% of patients with Stage III EC will survive for five years or more, and this declines drastically at Stage IV, with only 15% of patients surviving longer than five years.[2] Fewer than half (46.5%) of patients with Stage IV EC will survive for more than one year.[14, 28]

Table 3: FIGO cancer staging for EC

FIGO stage	Description
I	The cancer is confined to the uterus. The cancer may have grown from the endometrium into the myometrium.
II	The cancer has spread from the body of the uterus and is growing into the supporting connective tissue of the cervix, but it has not spread outside the uterus.
III	The cancer has spread outside the uterus and/or to the fallopian tubes or ovaries vagina or to the tissues that surrounding tissues around the uterus. It may have also spread to lymph nodes around the aorta but not too distant sites.
IVA	The cancer has spread to the inner lining of the rectum or urinary bladder. It may have spread to nearby lymph nodes but has not spread to distant sites.
IVB	The cancer has spread to inguinal (groin) lymph nodes, the upper abdomen, the omentum, or to organs away from the uterus, such as the lungs, liver, or bones. The cancer can be any size and it might or might not have spread to other lymph nodes.

Abbreviations: EC: endometrial cancer; FIGO: International Federation of Gynaecology and Obstetrics.
Source: American Cancer Society.[34]

Recurrent disease

Irrespective of stage, patients with EC can experience disease recurrence, defined as disease that cannot be detected after primary treatment, but then is radiologically or histologically detected again at a later point in time.[35] Overall, an estimated 13% of EC patients will experience disease recurrence in their lifetime, with the majority of recurrences occurring within three years post-treatment.[3] Prognosis drastically worsens in the recurrent setting with only 20% of patients surviving for five years or more, versus 89% of patients without disease recurrence.[3-5]

dMMR/MSI-H EC

dMMR/MSI-H is a molecular biomarker indicating the presence of a defective DNA repair process (Figure 2).[36] EC is reported to have the highest incidence of dMMR/MSI-H across all solid tumours, with approximately 23% of all EC cases classified as dMMR/MSI-H.[18, 37, 38]

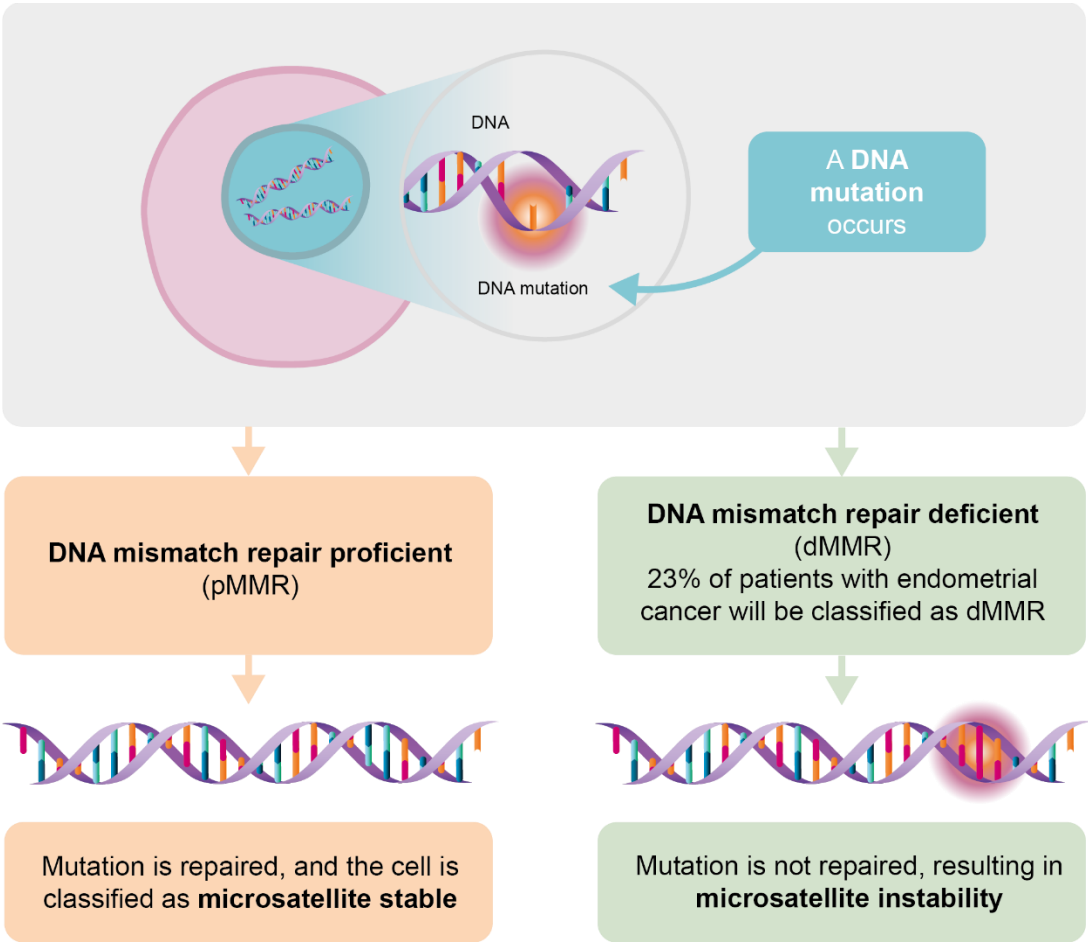
DNA mismatch repair (MMR) is a cellular process responsible for identifying and repairing mismatched bases that occur during DNA replication and genetic recombination.[23, 36] The system consists of DNA MMR proteins, which repair insertions or deletions of abnormal DNA within microsatellites (repetitive non-coding DNA sequences) (Figure 2).[36]

Mutations in the genes that code for these proteins can result in a defective MMR process which results in the accumulation of abnormal mutations.[36] This can be caused by sporadic mutations in the genes encoding the MMR proteins, or through inherited conditions such as Lynch

syndrome, which is the result of a germline mutation in the genes encoding several MMR proteins.[23] When one or more of these MMR proteins are dysfunctional, or are not expressed, this results in dMMR. Otherwise, the cancer is considered MMR-proficient [pMMR]) and microsatellite stable (MSS) (Figure 2).[36]

Microsatellite instability (MSI), a change in the length of repetitive sequences in tumour DNA compared with normal DNA, is the phenotypic (observable characteristic) result of dMMR.[39] MSI can be further characterised as high or low: if two or more DNA repeats are altered, this is specifically defined as MSI-H; if there is only one mutated sequence, this is considered microsatellite instability-low (MSI-L).[36]

Figure 2: The mechanism of action of the DNA MMR system and dMMR/MSI-H



Abbreviations: dMMR: DNA mismatch repair deficiency; MSI-H: microsatellite instability-high; MSS: microsatellite stable; pMMR: DNA mismatch repair proficient.
Source: Adapted from Eso *et al.* (2019).[40]

dMMR/MSI-H disease has one of the highest mutational loads versus other molecular subtypes, and is highly immunogenic, with increased levels of circulating tumour infiltrating lymphocytes and high expression of immune checkpoint molecules.[23, 39] This is important, as dMMR/MSI-H tumours are therefore more likely to respond to immuno-oncology (I–O) treatment, including anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) therapy such as dostarlimab.[23]

Evidence for this has been observed in other cancers, where patients with dMMR/MSI-H disease have experienced improved responses to I-O therapy, compared to patients with pMMR disease.

In KEYNOTE-016, a Phase 2 study of pembrolizumab in patients with progressive metastatic colorectal cancer, as well as other cancers, pembrolizumab demonstrated an objective response rate (ORR) of 40% in patients with dMMR/MSI-H disease versus 0% in patients with pMMR/MSS disease.[41]

Consequently, dMMR/MSI-H EC represents a subgroup where I-O therapy with dostarlimab is most effective.[23]

dMMR/MSI-H testing in the UK

In the UK, recently published NICE diagnostics guidance DG42 recommends that individuals with EC should undergo genetic testing for Lynch syndrome.[18] Lynch syndrome type II (also known as hereditary non-polyposis colorectal carcinoma [HNPCC] syndrome), accounts for up to 3% of all EC cases.[42] Lynch syndrome is a hereditary condition caused by mutations in the MMR genes, that predisposes women to developing EC throughout their lifetime. Whilst the general population risk of developing EC is 2%, women with Lynch syndrome have a 30-60% lifetime risk of developing EC.[12, 43]

NICE DG42 states that all patients with EC should be tested for dMMR/MSI-H using immunohistochemistry (IHC) testing, and if indicative of dMMR/MSI-H, patients are offered further germline genetic testing to confirm Lynch syndrome.[18] IHC testing is a simple, inexpensive technique already routinely used within the NHS to test for dMMR/MSI-H in other cancers, including colon cancer.[44]

UK clinical expert opinion sought by GSK for this submission agreed that IHC would be the preferred testing approach for dMMR/MSI-H EC and that all patients eligible for treatment with dostarlimab would receive dMMR testing as a result of this guidance.[16] Consultation with NHS England (NHSE) via an NHSE surgery also confirmed the availability of dMMR testing across England, and that access to testing will not be a barrier to accessing dostarlimab upon reimbursement. Consequently, dMMR testing via IHC will soon become standard of care for all patients with EC, and no additional diagnostic tests will be required to facilitate the prescribing of dostarlimab beyond those already conducted for patients with EC in UK NHS clinical practice.

Use of immunotherapy in dMMR/MSI-H disease

dMMR/MSI-H disease has one of the highest mutational loads versus other molecular subtypes, and is highly immunogenic, with increased levels of circulating tumour infiltrating lymphocytes and high expression of immune checkpoint molecules.[40] This high number of tumour antigens within the tumour microenvironment observed in dMMR/MSI-H tumours suggests these cancers may be more likely to respond to immuno-oncology (I–O) treatment, including anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) therapy such as dostarlimab.[23]

Evidence for this has been observed in other cancers, where patients with dMMR/MSI-H disease have experienced improved responses to I-O therapy, compared to patients with pMMR disease. KEYNOTE-016 was a Phase 2 single arm study of pembrolizumab in patients with progressive metastatic colorectal cancer, as well as other cancers. In the study pembrolizumab demonstrated an ORR of 40% in patients with dMMR/MSI-H disease versus 0% in patients with pMMR/MSS disease.[41]

Consequently, dMMR/MSI-H EC represents an extremely promising, biomarker selected patient population for dostarlimab.[23]

B.1.3.3 Epidemiology

There are an estimated 7,539 new patients diagnosed with EC in England every year.[12] This submission focusses on a small proportion of these patients – those with recurrent or advanced dMMR/MSI-H EC that has progressed on or after platinum-based chemotherapy. This is a small, well-defined proportion of the total number of patients with EC, and reflects those patients with the poorest prognosis, and critical unmet need.

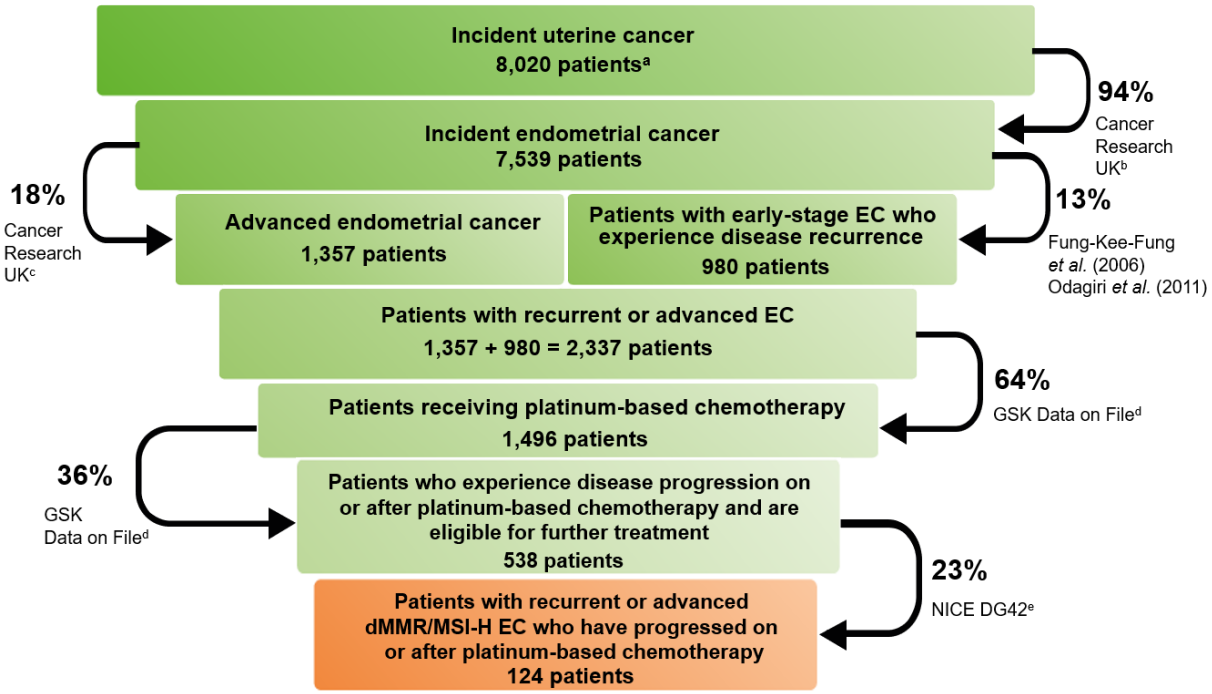
Approximately 18% of EC patients will be diagnosed with advanced EC (Stage III or IV) at first presentation, additionally approximately 13% of patients who are diagnosed at early stages of EC will later experience disease recurrence.[3, 5, 33] This means that approximately 2,337 patients will be diagnosed with recurrent or advanced EC in England each year. Of these, UK clinical expert opinion sought by GSK estimates that approximately two in three of these patients (64%) will receive first-line treatment with platinum-based chemotherapy for their disease.[16]

Regrettably, almost all patients who receive first-line platinum-based chemotherapy for recurrent or advanced EC will subsequently experience disease progression – in this setting, patients are no longer treated with curative intent, and disease progression is inevitable. The majority of patients receiving first-line platinum-based chemotherapy will never receive a subsequent line of treatment, and will have already died, or will be too severely unwell to receive further treatment with chemotherapy or hormone therapy. UK clinical expert opinion indicates that only one in every three patients (36%) who receive first-line platinum based chemotherapy will be eligible for further treatment with chemotherapy or hormone therapy, equating to approximately 538 patients in England every year.[16]

UK RWE evidence collected by GSK found that [redacted]% of patients received a chemotherapy subsequent to first-line platinum based chemotherapy.[13] It is likely that the discrepancy between the [redacted]% derived from the RWE study and the 36% from UK clinical expert opinion may be due to patients receiving hormone therapy in this setting within UK clinical practice, which could not be captured in the RWE study (see Section B.2.3.2).[13, 16]

Of the 538 patients with recurrent or advanced EC in England that suffer disease progression on or after platinum-based chemotherapy and are eligible for further treatment with chemotherapy or hormone therapy, approximately 23% will be classified with dMMR/MSI-H EC and will be eligible for treatment with dostarlimab.[18] This means that approximately 124 new patients will be eligible for treatment with dostarlimab in England each year. These assumptions are detailed in Figure 3 below.

Figure 3: Estimated dostarlimab-eligible patient population numbers in England



Footnotes: [a] 7,862 incident uterine cancer cases in 2017, adjusted to 2021 using an annual general population growth rate of 0.5%.[18, 45]
Abbreviations: DG: diagnostics guidance; dMMR: DNA mismatch repair deficiency; EC: endometrial cancer; MSI-H: Microsatellite instability-high; NA: not applicable.
Source: Fung-Kee-Fung *et al.* (2006);[3] Odagiri *et al.* (2011);[5] [a] Cancer Research UK;[33] [b] Cancer Research UK;[46] [c] Cancer Research UK;[33] [d] GSK Data on File;[16] [e] NICE DG42.[18]

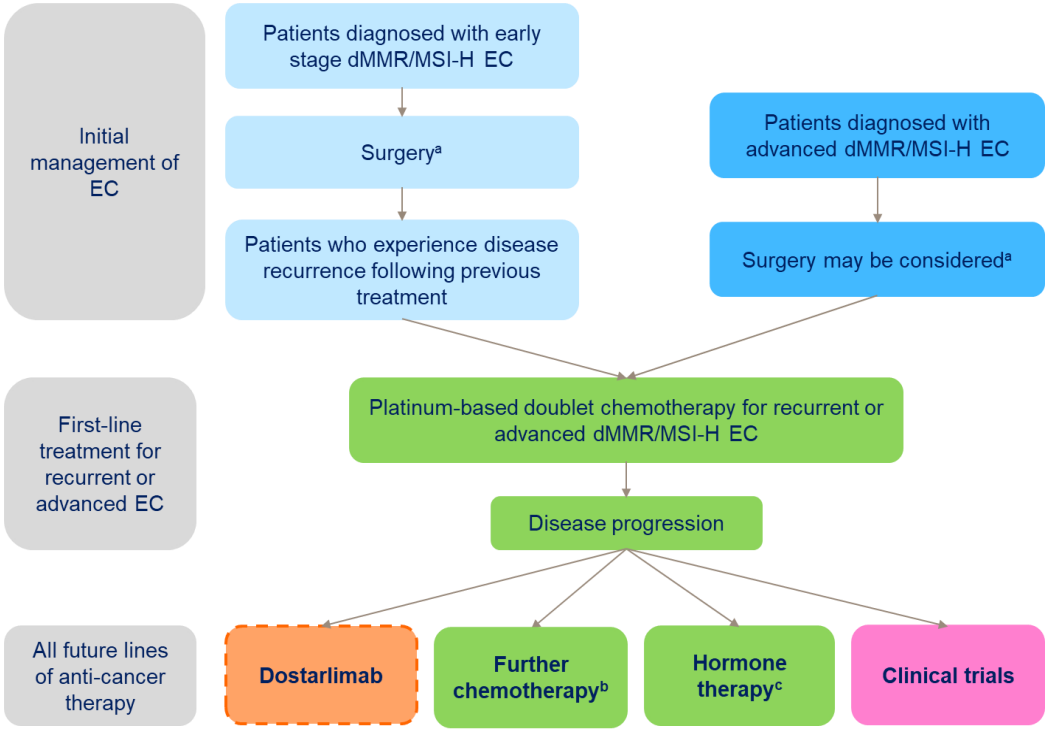
B.1.3.4 Clinical care pathway

Clinical guidelines for EC

There are a number of clinical guidelines available for the management of EC, however, they present very limited guidance for patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy. Clinical guidelines for the management of EC are available from the British Gynaecological Cancer Society (BGCS), the European Society of Medical Oncology (ESMO), the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO) and the European Society of Pathology (ESP).[14, 47, 48] There are no published NICE guidelines for EC.

Details of the current treatment pathway for patients with EC in the UK are presented in Figure 4 and below. These are based on the recommendations from key clinical guidelines, as well as UK clinical expert opinion and a RWE study conducted by GSK on clinical treatment patterns for patients with recurrent or advanced EC using linked patient-level health data available through the National Cancer Registry Analysis System (NCRAS) in England (hereafter referred to as the UK RWE study).[14, 47, 48]

Figure 4: Treatment pathway for patients with EC in the UK and the anticipated positioning of dostarlimab



Footnotes: [a] At any stage of disease, patients may also receive neoadjuvant or adjuvant radiotherapy, chemotherapy or hormone therapy, in addition to surgery. [b] Further chemotherapy may consist of carboplatin plus paclitaxel, doxorubicin or gemcitabine, carboplatin monotherapy, paclitaxel monotherapy, doxorubicin monotherapy, among others. [c] UK clinical expert opinion sought by GSK indicated that although not licensed, hormone therapy would consist of either letrozole or medroxyprogesterone acetate in this setting.
Abbreviations: dMMR: DNA mismatch repair deficiency; EC: endometrial cancer; MSI-H: microsatellite instability-high.

To provide context, a brief summary of the treatment pathway for early EC is provided in the sections below. This is followed by a more detailed summary of the treatments available for patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or following prior treatment with a platinum-containing regimen, as this is the indication of relevance to this submission.

B.1.3.4.1 Initial management of EC

The initial management of EC typically involves surgical treatment, which may include total hysterectomy (removal of the uterus and cervix) and bilateral salpingo-oophorectomy (removal of both ovaries and the fallopian tubes) with or without lymphadenectomy (removal of one or more groups of lymph nodes), depending on the stage of disease at diagnosis.[47, 48]

Patients with early stage EC (Stages I and II) receive surgery with curative intent. However, 13% of patients with early stage disease will experience disease recurrence in their lifetime, with the majority of recurrences occurring within the first three years of treatment.[3-5] Approximately 15–20% of patients are diagnosed with advanced EC.[33] For these patients, surgical treatment may still be considered, however, it is not likely to cure their disease.[47]

After surgery, patients at any stage of disease may also receive (neo)adjuvant radiotherapy or chemotherapy, depending on their risk factors.[47] Hormone therapy, including progestogens (e.g. megestrol, medroxyprogesterone acetate), tamoxifen and aromatase inhibitors (e.g. anastrozole,

letrozole) represent alternative treatment options for some patients at this early stage in the treatment pathway. These would typically be offered to patients who have high oestrogen or are HR+.[14]

B.1.3.4.2 Treatment for recurrent or advanced EC

First-line treatment for recurrent or advanced EC

For patients with recurrent or advanced EC, first-line platinum-based chemotherapy currently represents the last available standard of care treatment. In the UK, doublet chemotherapy with carboplatin plus paclitaxel is accepted as the standard of care in this setting. The RWE study conducted by GSK showed that [redacted]% of patients with recurrent or advanced EC received platinum doublet therapy as first-line treatment for recurrent or advanced EC, and carboplatin plus paclitaxel was the most commonly prescribed regimen.[13] However, as described previously, a majority of patients will progress after their first-line platinum based-chemotherapy.

All future lines of anti-cancer therapy – positioning of dostarlimab in this appraisal:

It is estimated that approximately one in three patients will be eligible for further treatment following disease progression on or after platinum-based chemotherapy for recurrent or advanced EC. In this setting, disease progression carries devastating and distressing consequences, and leaves patients facing a bleak prognosis with almost no hope of receiving further effective treatment.[48]

The lack of standard of care, or even a licensed treatment option at this stage, leads to patients feeling abandoned, with only extremely limited and inadequate treatment options based on unclear and inconsistent treatment guidelines. With a distinct lack of treatment options, the vast majority of patients are either treated with further chemotherapy, hormone therapy, or are enrolled into clinical trials. Each of these options is described in the following sections.

Chemotherapy

In UK clinical practice, most patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy will receive treatment with further chemotherapy however there is extremely limited consensus on which chemotherapy regimens to prescribe. BGCS guidelines recommend that re-challenge with carboplatin plus paclitaxel can be considered in fit patients.[14] However, ESMO guidelines note that there are no standard of care treatments in this setting, and currently used treatments are associated with disappointing response rates; only paclitaxel has consistently shown a response rate above 20% (and these response rates predate the use of paclitaxel as a prior treatment, meaning that they likely represent optimistic estimates for what might be achieved in UK clinical practice today).[14, 47] One study by Lincoln *et al.* (2003), reported an ORR for paclitaxel monotherapy of 27.3%.[49]

The UK RWE study conducted by GSK, using data from the NCRAS (see Section B.2.3.2) highlights the lack of consensus in UK clinical practice, with patients receiving a wide range of alternative chemotherapy regimens (Table 4).[13, 16]

Table 4: Ten most common chemotherapy regimens received by patients with recurrent or advanced EC following disease progression on platinum-based doublet chemotherapy

Chemotherapy regimen	Number of patients who received a regimen after their first doublet platinum regimen, n (%) (N=[redacted]) ([redacted]%)
Carboplatin plus paclitaxel	[redacted]
Carboplatin plus PLD	[redacted]
PLD monotherapy	[redacted]
Paclitaxel monotherapy	[redacted]
Carboplatin monotherapy	[redacted]
Cisplatin plus doxorubicin	[redacted]
Doxorubicin monotherapy	[redacted]
Cisplatin monotherapy	[redacted]
Carboplatin plus gemcitabine	[redacted]
Carboplatin plus doxorubicin	[redacted]

Abbreviations: EC: endometrial cancer; PLD: pegylated liposomal doxorubicin.
Source: GSK Data on File.[13]

Hormone therapy

UK clinical expert opinion sought by GSK suggests that hormone therapy, such as medroxyprogesterone acetate or letrozole, may also be a treatment option for a small select number of patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy.[16] These patients may be treated with hormone therapy despite the fact that BGCS guidelines highlight that there is no evidence that hormone therapy confers any survival benefit in the post-platinum setting.[14] This is substantiated by the results of a targeted literature review conducted by GSK (detailed in Appendix L), which did not identify any published evidence for hormone therapy in patients with recurrent or advanced EC that have received prior platinum-based chemotherapy.

Furthermore, UK clinical experts indicated that survival with hormone therapy would not be expected to exceed that observed in the UK RWE study, estimating that the median PFS and OS for hormone therapy in this setting would be approximately 3 months and approximately 6 months,[16] respectively, whereas median PFS associated with the chemotherapy regimens that constitute current clinical management in the UK RWE study is [redacted] (95% CI: [redacted], [redacted]) months and median OS is [redacted] months (95% CI: [redacted], [redacted]).[13]

Clinical trials

Finally, UK clinical expert opinion sought by GSK during the development of this submission highlighted that at this stage of treatment, given the distinct absence of an established standard of care, they would actively seek to enrol their patients in a clinical trial, due to the disappointing outcomes and toxicity associated with the limited treatment options that are currently available in clinical practice.[16] ESGO/ESTRO/ESP guidelines also note that clinical trial participation should be offered to all patients with relapsed disease, highlighting the inadequacy of currently available treatments.[48]

B.1.3.5 Limitations of current treatment and unmet need

Limited survival associated with current treatments

Sadly, patients with recurrent or advanced dMMR/MSI-H EC that have experienced disease progression on or after platinum-based chemotherapy face a distressing and bleak prognosis, regardless of which current treatment regimen they receive, and there is no evidence that hormone therapy confers any survival benefit in the post-platinum chemotherapy setting.[14] UK clinical experts have agreed that there is little expectation that either chemotherapy or hormone therapy are effective in this setting.[16]

The UK RWE study conducted by GSK (see Section B.2.3.2) found that patients in this setting have a median OS of just [redacted] months (95% CI: [redacted], [redacted]) following the initiation of further chemotherapy, and only [redacted]% and [redacted]% of patients were still alive after one and two years, respectively (Figure 5).[13]

Figure 5: UK RWE OS for patients with recurrent or advanced EC who received further chemotherapy following disease-progression on or after platinum-based chemotherapy

Abbreviations: CI: confidence interval; EC: endometrial cancer; OS: overall survival; RWE: real-world evidence.
Source: GSK Data on File.[13]

Patients face even worse PFS; the UK RWE study found that patients had a median PFS of just [redacted] months (95% CI: [redacted], [redacted]) from the initiation of 2L chemotherapy (using time to next treatment [TTNT] as a proxy for PFS). Only [redacted]% of patients were progression-free one year after the initiation of treatment, and this number dropped to just [redacted]% of patients after two years (Section B.2.4.5.2).[13]

Data from the published literature paint a similarly devastating picture for patients with recurrent or advanced EC following disease progression on platinum-based chemotherapy. Various clinical trials have reported that patients have a median OS of less than one year, with median PFS ranging from three to six months.[6-11] Published clinical outcomes for patients in this setting according to treatment are summarised in Section B.2.4 and Appendix D.5.2 and D.5.3.

Toxicity and HRQoL burden of further chemotherapy

Alongside the extremely limited clinical benefit, cytotoxic chemotherapy regimens are also associated with a number of harmful and debilitating side effects, including leukopenia, neutropenia, anaemia, fatigue, nausea, vomiting and alopecia.[30,10] UK clinical expert opinion sought by GSK has highlighted the toxicity burden of chemotherapy that lasts well beyond the duration of treatment, and has a detrimental impact on HRQoL for patients with EC.[16]

The substantial detrimental impact of chemotherapy was highlighted in the PORTEC-3 trial, where patients completed the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30, an internationally validated HRQoL questionnaire for cancer.[50] Patients with EC that received first-line platinum-based chemotherapy (in addition to radiotherapy) reported significantly lower scores (worse functioning) across most EORTC QLQ-C30 functioning scales, and significantly higher symptom scores (worse symptoms), versus patients receiving radiotherapy alone, following completion of radiotherapy and at Month 6.[50] Notably, these patients were only receiving their first-line of platinum-based chemotherapy. There is little reason to suggest that the patients relevant to this submission, who have already received prior treatment with platinum-based chemotherapy, would not experience at least a comparable decline in HRQoL on initiation of further chemotherapy treatment.

The toxicity burden of chemotherapy for patients with recurrent or advanced EC in the post-platinum setting was demonstrated in the ZoptEC trial, which found that [redacted]% of patients receiving doxorubicin experienced either a treatment emergent adverse event (TEAE) or treatment-related TEAE of ≥ Grade 3 severity. [8-10] According to the Common Terminology Criteria for Adverse Events (CTCAE), a Grade 3 AE represents an event which is *"severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limited self-care activities of daily living".*[51]

Severe unmet need for patients

The lack of effective treatment options for patients with recurrent or advanced dMMR/MSI-H EC that have progressed on or after platinum-based chemotherapy may have a substantially detrimental impact on patients and their families, leaving them feeling underserved and abandoned. There is a crucial unmet need for the introduction of new effective treatment options to be routinely available for these patients.

The interim introduction and availability of nivolumab via the CDF, despite a lack of data for its use in this patient population, highlights the severity of the unmet need for dMMR/MSI-H EC patients, and the enthusiasm within the UK clinical community for access to an I-O therapy for these patients. The introduction of a licensed, scientifically supported treatment option would be preferred by UK clinicians, given the additional data available when making a prescribing decision.

B.1.3.6 Dostarlimab

Dostarlimab is an I-O therapy and the first licensed PD-1 inhibitor monotherapy for patients with EC in the UK. Dostarlimab is positioned as a treatment option *for adult patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or following prior treatment with a platinum containing regimen*.[1] This is aligned with the marketing authorisation for dostarlimab, and the patient population included within the pivotal GARNET trial (see Section B.2.3.1).

As a novel and innovative I-O therapy in EC, the introduction of dostarlimab represents a clinically significant change in the management of patients with recurrent or advanced dMMR/MSI-H EC in the post-platinum chemotherapy setting.

In the GARNET trial (see Section B.2.3.1), treatment with dostarlimab resulted in additional survival for patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy, which has led to substantial excitement in the clinical community. Overall, [redacted]% of patients treated with dostarlimab were still alive after one year, and [redacted]% of patients were still alive after two years. In comparison, RWE in the UK for patients receiving a range of chemotherapies found that only [redacted]% and [redacted]% of patients were alive after one and two years, respectively. These survival results represent a truly clinically meaningful benefit for patients, who are otherwise at the end of their lives in current UK clinical practice.

Notably, in other cancers, I-O therapies have been shown to result in extended treatment benefits and long-term remission even after treatment discontinuation, offering a substantially improved prognosis for many patients.[52] Indeed, the long-term benefits of I-O therapies have been demonstrated across multiple indications including melanoma, lung, head and neck, where patients who discontinued therapy had durable responses that extended beyond the end of treatment.[53] Given this trend, it is reasonable to believe some patients who respond to dostarlimab may continue to experience extended treatment benefits and long-term remission beyond the two-year follow-up in the GARNET trial to date.

The introduction of dostarlimab would represent a shift in the treatment armamentarium for clinicians and patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or after platinum-based chemotherapy. Patient groups have shared that dostarlimab would provide hope to those who currently feel abandoned and currently face an extremely distressing prognosis with almost no chance of receiving effective treatment.

B.1.3.6.1 Anticipated positioning of dostarlimab in UK clinical practice

At a recent advisory board UK clinicians agreed that in clinical practice, dostarlimab is expected to be a treatment for patients who would otherwise receive further chemotherapy or hormone therapy, which would represent the most relevant comparators for this submission. Based on this anticipated positioning, a range of further chemotherapy regimens represent the most relevant comparators to dostarlimab in this submission, alongside hormone therapy in some patients.

As a result of the lack of definitive standard of care in this setting and the wide range of treatments used, in the base case economic analysis for this appraisal, GSK have primarily considered a comparison with a basket of the most commonly used chemotherapy regimens representing current clinical management in UK clinical practice, using data collected via the UK RWE study detailed in Section B.2.3.2.[13]

The UK RWE comparison incorporates the NICE final scope comparators as well as the most utilised chemotherapy regimens in UK clinical practice, which include carboplatin plus doxorubicin and carboplatin plus gemcitabine, amongst others. The identification of treatment regimens in the UK RWE study other than those included in the NICE final scope demonstrates the lack of consensus for the management of recurrent or advanced EC that has progressed on or after platinum-based chemotherapy.

In addition, GSK have considered individual comparisons in scenario analyses between

dostarlimab and the individual chemotherapy regimens listed in the NICE final scope for which published data exist.

Hormone therapy is included as a comparator in this submission, since it is included in the NICE final scope and has been confirmed as an appropriate comparator by UK clinical experts.[16] UK clinical experts agreed that medroxyprogesterone acetate and letrozole represent the most relevant hormone therapies used in this setting in UK clinical practice. However, as detailed in Section B.2.2 and B.2.7.3, there was no data identified for hormone therapy in patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy, meaning that any indirect comparisons are difficult, and would be associated with substantial limitations. It is also important to reiterate that there is no published evidence that hormone therapy provides any survival benefit in the post-platinum setting for this defined group of patients.[14]

The NICE final scope also lists BSC as an additional comparator, but GSK does not consider this to be relevant to this submission. BSC may be given as add-on therapy for patients with current or advanced EC in the post-platinum setting receiving further chemotherapy treatment, and it is anticipated that it may also be given to patients receiving dostarlimab, thus would in effect cancel one another out within the context of an economic analysis. Dostarlimab would not replace the use of BSC, and therefore BSC should not be considered a relevant comparator to dostarlimab in this submission.

B.1.4 Equality considerations

Due to the lack of effective treatment options for patients with recurrent or advanced dMMR/MSI-H EC who progress on or after platinum-based chemotherapy, feedback from UK clinical experts suggests that many clinicians have no choice but to seek to enrol these patients into clinical trials.[16] However, clinical trials are time bound, and the distribution, enrolment criteria and number of trial sites are restricted. Moreover, clinical trials are generally only available to patients treated in larger hospitals or near larger trial sites and are unlikely to be an option for patients in more rural areas of the UK. As such, the lack of nationally funded treatment options represents a possible equity concern.

Pembrolizumab is an alternative I-O therapy to dostarlimab, that has demonstrated efficacy for patients with recurrent or advanced EC who progress on or after platinum-based chemotherapy. However, it is an unlicensed therapy in Europe, and during the recent NICE scoping workshop, it was highlighted that pembrolizumab is currently only available in the private market in the UK. This represents an equity issue, whereby it is only available for patients who are able to afford the cost of treatment or are covered via private health insurance.

The availability of dostarlimab as a licensed, nationally funded treatment option on the NHS for patients whose only alternative options for receiving active treatment are via entry into a clinical trial or via private treatment with pembrolizumab would therefore help to address these equity issues.

B.2 Clinical effectiveness

Summary of the clinical effectiveness evidence

- The clinical effectiveness evidence for dostarlimab comprises GARNET: an ongoing open-label, single-arm, multicentre, Phase I study investigating the efficacy and safety of dostarlimab in patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy.[54]
- As GARNET is a single-arm trial, there is an absence of head-to-head data versus current clinical management. A clinical systematic literature review (SLR) for comparator evidence was conducted however a distinct paucity of data was identified. Most studies in the relevant patient population were observational studies, where patient characteristics and Kaplan-Meier (KM) survival data were poorly reported, limiting the quality, and therefore increasing the uncertainty, of any potential indirect treatment comparisons (ITCs). Moreover, due to a lack of standardised clinical guidelines and through discussions with UK clinical experts, it is clear that there is no definitive 'standard of care' for this population, resulting in a plethora of different treatment options being used across the UK.
- To address this, and to provide a more accurate representation of the current clinical management for recurrent or advanced EC that has progressed on or after platinum-based chemotherapy in the UK, a RWE study was conducted by GSK using NCRAS data. The RWE study included similar patients to those in GARNET who received a range of chemotherapy regimens, representative of current clinical treatment paradigms in the UK (N=[redacted]). Given the large sample size of this study, together with the close alignment to the patient characteristics in the GARNET trial, and the real-world representation of current clinical management in this difficult-to-treat population, this UK RWE study serves as the primary comparative efficacy evidence to dostarlimab in this submission.[13] In order to investigate the impact of any remaining differences between the two populations, a matching-adjusted indirect comparison (MAIC) of overall survival (OS) between GARNET and the UK RWE study was also conducted (see Section B.2.7.1).
- For completeness, a series of ITCs have been conducted between dostarlimab and the individual chemotherapy comparators listed in the NICE final scope where possible, based on available published data identified in the clinical SLR. Given the limitations associated with these analyses, they are provided for completeness as supportive comparative efficacy evidence only (see Section B.B.2.7.2.1 and Section B.B.2.7.2.2).

The GARNET study

- The pivotal GARNET study is the largest prospective evaluation of an anti-PD-1/L1 monotherapy in patients with recurrent or advanced EC to date, including 129 patients with recurrent or advanced dMMR/MSI-H EC who had progressed on or after platinum-based chemotherapy in the intention-to-treat (ITT) population.
- The co-primary endpoints of GARNET are objective response rate (ORR) and duration of response (DOR), while secondary endpoints include progression-free survival (PFS), OS, as well as health-related quality of life (HRQoL) and safety.
- Based on strong efficacy results from GARNET, instead of conducting a Phase III trial in the post-platinum setting, the Phase III RUBY trial is underway to evaluate the efficacy and safety of dostarlimab in combination with carboplatin plus paclitaxel, as a first-line treatment for patients with recurrent or primary advanced (Stage III or IV) dMMR/MSI-H EC versus carboplatin plus paclitaxel alone.[55]

Response rates for patients receiving dostarlimab versus current clinical management

- In the GARNET efficacy population (n=[redacted]), dostarlimab demonstrated clinically meaningful and durable anti-tumour activity, with an objective response rate (ORR) of [redacted]% ([redacted]) and

a disease control rate (DCR) of [redacted]% ([redacted]). This represents a marked increase compared to current clinical management. European Society of Medical Oncology (ESMO) guidelines highlight that for patients with advanced EC recurring after first-line chemotherapy, only paclitaxel has consistently shown a response rate >20%, less than half the ORR achieved by dostarlimab.[47] However, one study by Lincoln *et al.* (2003), reported an ORR for paclitaxel monotherapy of 27.3%.[49]

- Importantly, the responses to dostarlimab were durable; [redacted]% ([redacted]) of responders maintained a response up to Month 12, and by Month 18, [redacted]% ([redacted]) of responders were still experiencing an ongoing response to dostarlimab.

PFS and OS for patients receiving dostarlimab versus current clinical management

- Results for PFS from GARNET show a clear benefit in favour of dostarlimab and paint current clinical management in a harrowing light. At Month 12, [redacted]% of patients treated with dostarlimab in the ITT population (n=129) were progression-free, compared to just [redacted]% of patients treated with current clinical management from the UK RWE study. At Month 24, [redacted]% of patients treated with dostarlimab remained progression-free, compared with just [redacted]% in the UK RWE study (see Section B.2.4.5).
- Patients in GARNET also experienced a remarkable survival benefit compared with current clinical management in the UK. By Month 12, [redacted]% of patients treated with dostarlimab in the ITT population (n=129) were still alive versus just [redacted]% of patients in the UK RWE study. By Month 24, [redacted]% of patients treated with dostarlimab were still alive. In contrast, the UK RWE study showed no evidence of a long-term survival benefit with current clinical management; by Month 24, just [redacted]% of patients were still alive – [redacted] of the proportion of patients treated with dostarlimab that were still alive by Month 24 (see Section B.2.4.6). The results of the OS MAIC were consistent with this naïve comparison, demonstrating a similar magnitude of OS benefit for patients treated with dostarlimab versus current clinical management (unadjusted hazard ratio [HR]: [redacted]; 95% CI: [redacted]; adjusted HR: [redacted]; 95% CI: [redacted]) (see Section B.2.7.1).

HRQoL, safety and tolerability associated with dostarlimab

- In terms of HRQoL, the GARNET study showed that treatment with dostarlimab preserved patient-reported HRQoL from baseline. Key disease-related symptom subscales, such as pain and fatigue showed a positive trend of improvement throughout the study.
- Dostarlimab was also shown to be well-tolerated and associated with a manageable AE profile in line with other currently licensed anti-programmed cell death ligand 1 (PD-L1) therapies. Treatment emergent adverse event (TEAEs) related to treatment were generally low grade (only [redacted]% of patients reported any Grade ≥3 treatment-related TEAE), and discontinuation as a result of treatment-related AEs was low ([redacted]%). The most frequent treatment-related TEAEs were diarrhoea ([redacted]%) and asthenia ([redacted]%).
- In contrast, cytotoxic chemotherapy regimens are associated with debilitating AEs. Whilst safety data were not collected in the UK RWE study, data from the ZoptEC study report that 96.4% of patients receiving doxorubicin monotherapy experienced treatment-related TEAEs (compared to [redacted]% in GARNET), and [redacted]% of patients reported any Grade ≥3 TEAE (compared to [redacted]% in GARNET).[8-10]

Conclusion

- The remarkable survival outcomes for patients in GARNET, combined with a well-tolerated safety profile, mean that the introduction of dostarlimab in the UK would provide hope to patients with recurrent or advanced dMMR/MSI-H EC in the post-platinum chemotherapy setting who currently feel abandoned and face an extremely distressing prognosis, with almost no chance of receiving effective treatment.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant clinical evidence for the efficacy and safety of dostarlimab and the chemotherapy comparators listed in the NICE final scope for the treatment of recurrent or advanced EC that has progressed on or after platinum-based chemotherapy .

In total, 3,077 publications were screened, of which 148 publications were reviewed at the full-text stage. After exclusion of publications not meeting the eligibility criteria, 23 publications (reporting on 13 unique studies) were included in the SLR. Full details of the SLR, including the search strategy, study selection process and detailed results, are presented in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1.1 Dostarlimab (GARNET)

Of the 13 studies included in the clinical SLR, one clinical trial, GARNET (NCT02715284), was identified for dostarlimab and this represents the pivotal clinical trial for dostarlimab in this indication.[56-58] Further details on the GARNET trial are presented in Section B.2.3.1.

B.2.2.1.2 Comparators (NICE final scope)

The remaining 12 studies included in the clinical SLR investigated relevant chemotherapy regimens in patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy. These trials included patients receiving carboplatin plus paclitaxel, paclitaxel monotherapy and doxorubicin monotherapy. No studies were identified for carboplatin monotherapy.

In addition, hormone therapy was not included in the original SLR, because it was not considered to be a relevant comparator to dostarlimab at the time the review was conducted. Following the inclusion of hormone therapy in the NICE final scope and discussions with UK clinical experts that indicated that hormone therapy would be considered in a small subset of patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or after platinum-based chemotherapy, a targeted literature review of PubMed was conducted to identify relevant evidence for hormone therapy, but no suitable studies were identified (see Appendix L).

For the studies that were identified in the clinical SLR for comparator therapies, there was a distinct paucity of reported data. Most studies in the relevant patient population were observational studies, where patient characteristics and KM survival data were poorly reported, limiting the quality, and therefore increasing the uncertainty, of any potential ITCs. Nevertheless, for completeness, a series of ITCs have been conducted between dostarlimab and the individual chemotherapy comparators listed in the NICE final scope where possible, based on available published data identified in the clinical SLR. Given the limitations associated with these analyses, they are provided for completeness as supportive comparative efficacy evidence only and are presented in Section B.2.7.

It should be noted that despite efforts made to identify alternative sources of data for hormone therapy and carboplatin monotherapy (as no relevant studies were identified in the literature), feedback from UK clinical experts strongly indicated that any data for patients not in the post-platinum chemotherapy setting would not be suitable to use as a proxy for these therapies. As

such, it was not possible to conduct any individual comparisons in terms of comparative efficacy between dostarlimab and carboplatin monotherapy or hormone therapy.

B.2.2.1.3 Current clinical management (UK RWE study)

Given the limitations of the studies identified in the clinical SLR for the comparators listed in the NICE final scope, and to provide a more accurate representation of the current clinical management for recurrent or advanced EC that has progressed on or after platinum-based chemotherapy in the UK, a RWE study was conducted by GSK using NCRAS data.[13] This study included a population of patients closely aligned to the patients in GARNET that received a range of chemotherapy regimens that represent current clinical treatment paradigms in the UK (N=[redacted]).

Given the large sample size of this study, together with the close alignment to the patient characteristics in the GARNET trial, and the real-world representation of current clinical management in this difficult-to-treat population, this UK RWE study serves as the primary comparative efficacy evidence in this submission and informs the base case cost-effectiveness analysis.

Full details of the UK RWE study are presented in Section B.2.3.2. To explore the impact of any potential remaining differences between the GARNET and UK RWE study patient populations, an ITC was conducted between GARNET and the UK RWE study for OS, and details of this analysis are presented in Section B.2.7.1.

An overview of the comparative efficacy evidence presented in this submission is presented in Table 5.

Note that not all of the comparative efficacy evidence was considered suitable for decision-making and therefore not all of the analyses have been included within the economic model. Full details of the comparative efficacy evidence included within the economic model are presented in Section B.3.

Table 5: Summary of the clinical effectiveness evidence presented in this submission

Therapy	Clinical evidence	Available comparative clinical evidence versus dostarlimab (GARNET)	Section of the submission
Primary evidence			
Dostarlimab	• GARNET	NA	Section B.2.3.2, Section B.2.4
Current clinical management	• UK RWE study	• Unadjusted comparison with the UK RWE study • OS[a] MAIC with the UK RWE study	Section B.2.3.2, Section B.2.4, Section B.2.7.1, Appendix D.5.1
Supportive evidence versus individual comparators			
Carboplatin plus paclitaxel	• Rubinstein *et al.* (2019)[59] • Mazgani *et al.* (2008)[60]	• PFS and OS MAIC with Rubinstein *et al.* (2019)[59] • PFS and OS MAIC with Mazgani *et al.* (2008)[60]	Section B.2.7.2.2, Section B.2.7.2.3, Appendix D.5.3
Paclitaxel monotherapy[b]	• McMeekin *et al.* (2015)[6]	• OS[c] MAIC with McMeekin *et al.* (2015)[6]	Section B.2.7.2.2, Section B.2.7.2.3, Appendix D.5.3
Doxorubicin monotherapy[b]	• ZoptEC[8-10] • McMeekin *et al.* (2015)[6] • Makker *et al*. (2013)[11] • Julius *et al*. (2013)[7]	• OS IPTW ITC versus ZoptEC[8-10] • PFS[d] ITC versus ZoptEC[8-10] • OS[c] MAIC with McMeekin *et al.* (2015)[6] • PFS and OS MAIC with Makker *et al*. (2013)[11] • OS[c] MAIC with Julius *et al*. (2013)[7]	Section B.2.7.2.1 Section B.2.7.2.2, Section B.2.7.2.3 Appendix D.5.2, Appendix D.5.3
Carboplatin monotherapy	No relevant published data were identified for carboplatin monotherapy in the indication of relevance to this submission.	NA – no evidence was identified for carboplatin monotherapy in the clinical SLR. Feedback from UK clinical experts strongly indicated that any data for patients not in the post-platinum chemotherapy setting would not be suitable to use as a proxy for patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy. As such, it was not possible to conduct an individual comparison between dostarlimab and carboplatin monotherapy based on the published literature for carboplatin monotherapy.	NA

		An economic scenario analysis has been conducted versus carboplatin monotherapy, assuming equal efficacy to doxorubicin monotherapy (detailed in Section B.3.8.3).	
Hormone therapy	No relevant published data were identified for hormone therapy in the indication of relevance to this submission.	NA – a targeted literature review of PubMed was conducted to identify relevant evidence for hormone therapy but no relevant studies in patients with recurrent or advanced EC who had progressed on or after platinum-based chemotherapy were identified. Additionally, hormone therapy use was not fully captured within the UK RWE study. Despite efforts to identify alternative sources of evidence to use as proxy, feedback from UK clinical experts strongly indicated that any data for patients not in the post-platinum chemotherapy setting would not be suitable to use as a proxy for hormone therapy. As such, it was not possible to conduct an individual comparison between dostarlimab and hormone therapy. An economic scenario analysis was conducted assuming that the efficacy of hormone therapy was equal to current clinical management in the UK RWE study (as detailed in Section B.3.8.3).	Section B.2.7.3 Appendix L
BSC	NA – BSC is not considered a relevant comparator to dostarlimab in this submission, and a comparison versus BSC has not been included for the reasons detailed in Table 1.		NA

Footnotes: [a] Due to the differences in PFS in GARNET versus TTNT in the UK RWE study, it was only possible to conduct a MAIC using a Cox proportional hazards model for OS between GARNET and the UK RWE study. [b] Patients in the McMeekin *et al.* (2015)[6] study received either paclitaxel or doxorubicin. Clinical expert opinion indicated that the efficacy between the two treatments is likely to be similar, and therefore it is appropriate to consider this as one combined arm that provides evidence for both paclitaxel monotherapy and doxorubicin monotherapy. [c] PFS curves for PFS were not reported in McMeekin *et al.* (2015) and Julius *et al.* (2013), meaning it was only possible to conduct OS MAICs versus these studies.[6, 7] [d] It was not possible to use IPTW to estimate a HR for PFS between dostarlimab and doxorubicin, due to differences in the definition of PFS and the timepoints of tumour assessments between GARNET and ZoptEC (detailed in Appendix D.5.2).[8-10]
Abbreviations: BSC: best supportive care; IPTW: inverse probability treatment weighting; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; NA: not applicable; OS: overall survival; PFS: progression-free survival; RWE: real-world evidence.

B.2.3 Summary of methodology of GARNET and the UK RWE study

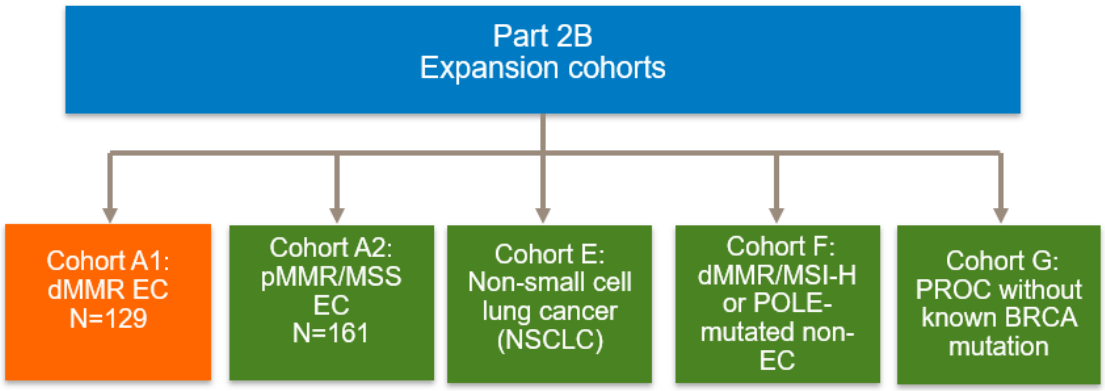
B.2.3.1 Dostarlimab (GARNET)

The clinical SLR identified one trial for dostarlimab in patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy: the GARNET trial, an open-label, single-arm, multicentre, non-randomised Phase I trial (NCT02715284).

GARNET was conducted in two parts: Part 1 of the study, which established the recommended dose for dostarlimab (dose escalation), and Part 2, which was conducted in two subparts (2A and 2B). Part 2A evaluated the safety and tolerability of dostarlimab in fixed-dose safety evaluation cohorts. Part 2B (the extension phase) investigated the efficacy of dostarlimab in five expansion cohorts according to the following tumour types: dMMR/MSI-H EC (Cohort A1), MMR-proficient/MSS EC (Cohort A2), non-small cell lung cancer (NSCLC) (Cohort E); dMMR/MSI-H or POLE-mutated non-EC (Cohort F) and platinum-resistant ovarian cancer (PROC) without known breast cancer susceptibility gene mutation (BRCA).[54]

This submission focuses solely on Part 2B, Cohort A1 of GARNET, the cohort of patients with recurrent or advanced dMMR/MSI-H EC, in alignment with the indication of relevance to this submission and the licensed indication for dostarlimab (Figure 6).

Figure 6: GARNET trial design



Abbreviations: BRCA: breast cancer susceptibility gene; dMMR: DNA mismatch repair deficiency; EC: endometrial cancer; MSS: microsatellite stable NSCLC: non-small cell lung cancer; pMMR: mismatch repair proficient; POLE: polymerase ε; PROC: platinum-resistant ovarian cancer.
Source: GSK Data on File.[54]

B.2.3.1.1 Summary of trial methodology

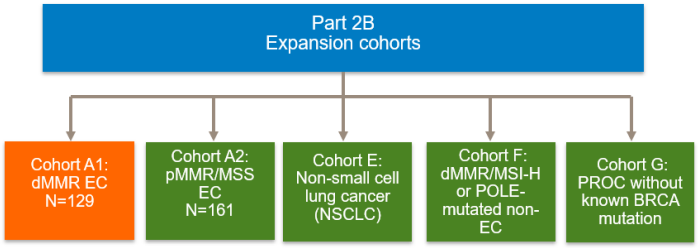
A summary of the trial methodology for the GARNET trial is presented in Table 6.

Table 6: Summary of methodology for GARNET trial

Study	GARNET (NCT02715284) (Oaknin *et al.* [2020])[56-58]
Location	International trial with centres in nine countries: • United Kingdom (nine sites) • Poland • Canada • Denmark

<table>
<tr><td></td><td colspan="3">France
Italy
Spain
United States</td></tr>
<tr><td>Trial design</td><td colspan="3">Ongoing, open-label, single-arm, multicentre, non-randomised Phase I trial</td></tr>
<tr><td>Population</td><td colspan="3">The extension phase of the GARNET trial enrolled five cohorts of patients:
Cohort A1: patients with recurrent or advanced dMMR/MSI-H EC that has progressed after treatment with a platinum-containing chemotherapy regimen
Cohort A2: patients with recurrent and advanced MMR-proficient/microsatellite stable (MSS) EC
Cohort E: non-small cell lung cancer (NSCLC)
Cohort F: dMMR/MSI-H or polymerase ε (POLE)-mutated non-EC
Cohort G: platinum-resistant ovarian cancer without known BRCA mutations
This submission will focus solely on Cohort A1, the cohort of patients with recurrent or advanced dMMR/MSI-H EC, in alignment with the indication of relevant to this submission and the licensed indication for dostarlimab.

Cohorts A2, E, F and G are not within the scope of this submission and they do not align with the marketing authorisation for dostarlimab. Therefore, the results of these cohorts will not be presented or discussed further within this submission.

Figure 7: Cohorts in the GARNET trial
 

Abbreviations: BRCA: breast cancer susceptibility gene; dMMR: DNA mismatch repair deficiency; EC: endometrial cancer; MSS: microsatellite stable NSCLC: non-small cell lung cancer; pMMR: mismatch repair proficient; POLE: polymerase ε; PROC: platinum-resistant ovarian cancer.
Source: GSK Data on File.[54]</td></tr>
<tr><td>Intervention(s)</td><td colspan="3">Dostarlimab</td></tr>
<tr><td>Comparator(s)</td><td colspan="3">NA (single-arm trial)</td></tr>
<tr><td>Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>Indicate if trial used in the economic model</td><td>Yes</td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="3">GARNET is the pivotal trial for dostarlimab in patients with recurrent or advanced dMMR/MSI-H EC. Cohort A1 is directly relevant to the decision problem as it included patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or following prior treatment with a platinum-containing regimen.</td></tr>
</table>

	This is aligned with the licensed indication for dostarlimab and the population included in the NICE final scope (although it is important to note that patients eligible for dostarlimab *must have progressed on or following prior treatment with a platinum-containing regimen*, which is not explicitly listed in the final scope).
Eligibility criteria	A summary of inclusion and exclusion criteria are provided below. Full details of the eligibility criteria are presented within Appendix N.1. **Key inclusion criteria** • 18 years of age or older • Histologically or cytologically proven recurrent or advanced EC with measurable lesion(s) per RECIST v1.1 • Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 **Key exclusion criteria** • Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-programmed cell death-ligand 2 agent • Known uncontrolled central nervous system metastases and/or carcinomatous meningitis • Known additional malignancy that progressed or required active treatment within the last 2 years
Trial drugs and method of administration	Dostarlimab 500 mg via IV infusion every 3 weeks (Q3W) (Day 1 of each 21-day cycle) for the first 4 cycles, followed by dostarlimab 1000 mg via IV infusion every 6 weeks (Q6W) (Day 1 of each 42-day cycle) for all subsequent cycles.
Permitted and disallowed concomitant medication	**The following concomitant medications were disallowed:** • Systemic anticancer or biological therapy • Immunotherapy not specified in the protocol • Chemotherapy not specified in the protocol • Investigational agents other than dostarlimab • Radiation therapy within 3 weeks prior to study Day 1 and during study treatment • Any surgery that involves tumour lesions • Systemic glucocorticoids for any purpose other than to manage symptoms of suspected irAEs **The following concomitant medications were permitted:** • The use of inhaled steroids, local injection of steroids, and steroid eye drops • Live vaccines within 14 days prior to the first dose of study treatment; seasonal flu vaccines that do not contain live viruses
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoints were objective response rate (ORR) and duration of response (DOR) based on BICR using RECIST v1.1. Radiographic evaluations were conducted at week 12 after the first dose of dostarlimab, then every 6 weeks (±10 days) or as clinically indicated until month 12, and then every 12 weeks thereafter. ORR was defined as the proportion of patients who achieved a best overall response (BOR) of complete response (CR) or partial response (PR) per RECIST v1.1. Patients who did not have a post-baseline radiographic tumour assessment; who received post-baseline antitumour treatments (including surgery or radiation to the tumour lesions) other than the study treatments prior to reaching a CR or PR; or who died, progressed, or dropped out for any reason prior to reaching a CR or PR were counted as non-responders in the assessment of ORR.

	DOR was defined as the time from the first documentation of overall response leading to a confirmed CR or PR when confirmation was required by RECIST v1.1 until the time of first documentation of overall response of disease progression or death. Clinical deterioration was not considered as documented disease progression. Only tumour assessments performed before the start of any new anticancer treatment (including radiation therapy to the tumour lesion[s]) were considered in the assessment of DOR.
Secondary and exploratory outcomes (including scoring methods and timings of assessments)	The secondary endpoints were immune-related disease control rate (irDCR), immune-related disease control rate (irDOR), immune-related progression-free survival (irPFS), and immune-related objective response rate (irORR) using Immune-related Response Evaluation Criteria In Solid Tumors (irRECIST); PFS and DCR based on blinded independent central review (BICR) using RECIST v1.1; OS, and immunogenicity[a]. The timing and assessment of these endpoints are described below. **PFS and irPFS:** PFS time was defined as the time from the date of the first dose to the earlier date of assessment of disease progression or death by any cause in the absence of disease progression based on the time of first documentation of disease progression per RECIST v1.1. An irPFS time was defined as the time from the date of the first dose to the earlier date of assessment of immune-related progressive disease (irPD) event or death by any cause in the absence of disease progression based on the time of irPD event per irRECIST. PFS and irPFS times were defined as follows: *PFS (days) = Date of progressive disease (PD) or irPD event or death/Censoring – Date of First Dose + 1* Only tumour assessments performed before the start of any new anticancer treatment (including radiation therapy to the tumour lesion[s]) were considered in the assessment of PFS and irPFS. **DCR and irDCR:** Per RECIST v1.1, DCR was defined as the proportion of patients achieving BOR of confirmed CR, PR, or SD. Per irRECIST, irDCR was defined as the proportion of patients achieving immune-related best overall response (irBOR) of immune-related complete response (irCR), immune-related partial response (irPR), or immune-related stable disease (irSD) as assessed by the Investigator. **OS:** OS was defined as the time from the date of the first dose of study treatment to the date of death by any cause. Patients last known to be alive were censored at the date of the last known contact, as follows: *OS (days) = Date of death/Censoring – Date of the first dose + 1* **irORR:** Timings and assessment were as described for primary efficacy endpoint ORR. **irDOR:** Timings and assessment were as described for primary efficacy endpoint DOR. **EQ-5D-5L and EORTC QLQ-C30:** Patient-reported outcome (PRO) assessments (EQ-5D-5L and EORTC QLQ-C30 for all patients in Cohort A1 enrolled under protocol amendment 3 or subsequent amendments) were collected during scheduled visits i.e. every 3 weeks ±7 days for the first 12 weeks, in alignment with study drug administration, and every 6 weeks (±7 days) thereafter, in alignment with tumour imaging assessments, while the

	patient is receiving study treatment. Once a patient discontinues treatment, PRO assessments will be performed during the end-of-treatment (EOT) visit, the safety follow-up visit, and during the post-treatment follow-up period every 90 days (±14 days). **Other exploratory outcomes:** Other exploratory outcomes measured in the GARNET trial included changes in intra-tumoural cells and circulating biomarkers in the blood[a], profile of tumour-infiltrating lymphocytes (TILs), tumour cell characteristics including genomic alterations and/or circulating biomarkers prior to treatment with dostarlimab and to correlate them with clinical benefit[a].
Pre-specified subgroup analyses	Subgroup analyses were conducted for the primary endpoints of ORR and DOR based on BICR using RECIST v1.1 for histologic subtypes, disease stages, and lines of therapy.

Footnotes: [a] Additional details/timings and results for these outcomes can be found in the GARNET Clinical Study Report and are not presented within this submission.
Abbreviations: BICR: blinded independent central review; DCR: disease control rate; DOR: duration of response; EC: endometrial cancer; ECOG: Eastern Cooperative Oncology Group; EOT: end-of-treatment; EORTC QLQ-C30; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L: EuroQoL 5-dimensions 5-levels; irAE, immune-related adverse event; irCR: immune-related complete response; irDCR: immune-related disease control rate; irDOR: immune-related duration of response; irPD: immune-related progressive disease; irPFS: immune-related progression-free survival; irORR: immune-related objective response rate; (ir-)RECIST: (immune-related) Response Evaluation Criteria in Solid Tumours; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PD: progressive disease; PD-1/PD-L1: programmed cell-death ligand 1; PFS: progression-free survival; POLE: polymerase ε; PRO: patient reported outcome; TILs: tumour-infiltrating lymphocytes.
Source: GSK Data on File, GARNET clinical study report.[54]

B.2.3.1.2 Baseline characteristics

Baseline demographics and disease characteristics of the patients included in Cohort A1 of the GARNET trial are presented in Table 7. Two populations from the GARNET trial are relevant to this submission. The intention-to-treat (ITT) population (which is analogous with the safety analysis set) includes all patients that received at least one dose of dostarlimab, and informs the base case cost-effectiveness analysis in this submission. The efficacy population (at the time of interim analysis 2 [IA2]) (N=[redacted]) only includes patients who had measurable disease at baseline and who had at least 24 weeks follow-up to allow analysis of the response-related endpoints in GARNET (objective response rate [ORR], best overall response [BOR], disease control rate [DCR]), and is used in a sensitivity analysis. Further details of these analysis sets can be found in Section B.2.3.1. The ITT population represents the base case population in the economic analysis.

The mean age of patients in the ITT population of the GARNET trial was [redacted] years, with the majority of patients being <65 years old ([redacted]%) at the time of study entry. The majority of patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1 ([redacted]%) and a most recent FIGO stage of IV ([redacted]%). All of the patients had received at least one prior anti-cancer treatment, with the majority of patients ([redacted]%) receiving exactly one prior line of anti-cancer therapy.

Please note that both populations summarised below included a very small minority of patients (N=[redacted] in the ITT population) who were classified as MMR-unknown, rather than dMMR. Patients with MMR-unknown (MMR-unk) were those whose MMR status was not tested in the trial; however, the expectation is that all patients would be tested for dMMR status in clinical practice.

It is reasonable to assume that almost all of these patients would have tested positive for dMMR, had they been tested for dMMR, because they tested positive for MSI-H, which is the phenotypic presentation of dMMR.[36] This is evidenced by the fact that results remain similar when data from patients with MMR-unk but MSI-H tumours are pooled with those of subjects with dMMR tumours. Therefore, these populations (dMMR/MSI-H and MMR-unknown/MSI-H) are presented as one throughout the submission.

Table 7: Baseline demographics and disease characteristics of patients in GARNET

Characteristic	Efficacy population (N=[redacted])	ITT population (N=129)
Mean age, years (STD)	[redacted]	[redacted]
Age group, n (%)		
<65 years	[redacted]	[redacted]
65 to <75 years	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]
Unknown[b]	[redacted]	[redacted]
Weight, kg		
Median, (range)	[redacted]	[redacted]
BMI, kg/m^2		
Median, (range)	[redacted]	[redacted]
Height, cm		
Median, (range)	[redacted]	[redacted]
Serum creatinine		
Mean serum creatinine at baseline, µmol/L (STD)	[redacted]	[redacted]
ECOG PS, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Histology at diagnosis, n (%)		
Endometrioid carcinoma type I	[redacted]	[redacted]
Endometrial carcinoma type II	[redacted]	[redacted]
Serous carcinoma	[redacted]	[redacted]
Clear cell carcinoma	[redacted]	[redacted]
Squamous carcinoma	[redacted]	[redacted]
Undifferentiated carcinoma	[redacted]	[redacted]
Carcinosarcoma	[redacted]	[redacted]
Mixed carcinoma	[redacted]	[redacted]
Unspecified	[redacted]	[redacted]
Other	[redacted]	[redacted]

Histology unknown at time of diagnosis	[redacted]	[redacted]
Most recent FIGO stage, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Grade of disease at diagnosis, n (%)		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Prior anticancer treatment, n (%)		
Any prior anti-cancer treatment	[redacted]	[redacted]
Surgery	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
Number of prior lines of therapy, n (%)		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
≥4	[redacted]	[redacted]

Footnotes: [a] Includes American Indian or Alaska Native. [b] Includes 'Not reported'.
Abbreviations: BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynaecology and Obstetrics; IA2: interim analysis 2; ITT: intention-to-treat; STD: standard deviation.
Source: GSK Data on File.[13]

B.2.3.1.3 Statistical analysis and definitions of study groups

The analysis of the primary endpoint ORR analyses in GARNET included summary statistics, including the number of patients (n) and percentage for categorical variables and the number of patients, mean, standard deviation (STD), median, minimum, and maximum for continuous variables. Two-sided exact 95% confidence interval (CIs) based on the Clopper-Pearson method were provided.

The duration of response (DOR) primary endpoint analyses were performed using Kaplan-Meier (KM) methods and summarised by minimum, maximum, 25th, 50th (median), and 75th percentiles with associated 95% CIs, the number and percentage of events, and number and percentage of censored observations.

The null hypothesis that the true response rate is ≤20% (H0: p≤0.2) was tested against a 1-sided alternative of ≥40% (Ha: p≥0.4). With 65 participants treated, Cohort A1 has 92% power to rule out a ≤20% ORR (null hypothesis; expected ORR for conventional therapy) when the true ORR is 40% at the 2.5% type I error rate (1-sided). Based on a recent report that 6 of 9 participants with MSI-H EC achieved a clinical response following treatment with an anti-PD-1 antibody, the activity of dostarlimab in this participant population is expected to negate the necessity for a 2-

stage design, and thus, there was no interim analysis in this cohort. Under protocol amendment 5 (10th May 2019), the sample size of Cohort A1 was increased to 100 participants, with the potential for up to 165 participants, which allows the lower-limit boundary of the exact 95% CI excluding a response rate of 25% or less and assuming the observed ORR is 35%.

An overview of the statistical analysis sets analysed in GARNET is provided in Table 8.

Table 8: Statistical analysis sets in GARNET

Analysis set	Definition
ITT population/safety analysis set (N=129)	The ITT population/safety analysis set was defined as all patients who received any amount of dostarlimab regardless of follow-up time at the time of data cut-off of IA2. This population informs the base case cost-effectiveness analysis.
Efficacy population at IA2[a] (defined using RECIST v1.1 per BICR) (N=[redacted])	The IA2 efficacy population set by RECIST v1.1 per BICR was defined as all patients in the safety analysis set with measurable disease at baseline (defined as the existence of at least one target lesion at baseline tumour assessment by BICR) who had the opportunity for at least 24 weeks of tumour assessment at the time of IA2 (DCO 1st March 2020).
Immune-related efficacy population at IA2 (defined using irRECIST per Investigator's assessment) (N=[redacted])	The IA2 efficacy population set by irRECIST per Investigators' assessment was defined as all patients in the safety analysis set with measurable disease at baseline (defined as the existence of at least one target lesion at baseline tumour assessment by Investigators' assessment) who had the opportunity for at least 24 weeks of tumour assessment at the time of IA2. This population relates to the immune-related outcomes only, results of which are presented in Section B.2.4.7 (irPFS) and Appendix N.2. (immune-related response rates).

Footnotes: [a] A smaller number of patients were included in the efficacy population at the first interim analysis (N=72), however, these data are not presented within this submission, in favour of the data for the larger efficacy population at IA2, and the ITT population, where applicable.
Abbreviations: BICR: blinded independent central review; DCO: data cut off; IA2: interim analysis 2; irPFS: immune-related progression-free survival; ITT: intention-to-treat; RECIST v1.1: Response Evaluation Criteria in Solid Tumours version 1.1.
Source: GSK Data on File.[54]

B.2.3.1.4 Quality assessment

A quality assessment of the GARNET trial was carried out using the Critical Appraisal Skills Program (CASP) Risk for Bias Tool for non-RCTs.[61] This checklist focuses on three broad issues: Are the results of the study valid? (Section A) What are the results? (Section B) Will the results help locally? (Section C). The 12 questions that make up the tool are designed to help the researcher think about these issues systematically.

Overall, due to the lack of randomisation and the single-arm nature of the trial, GARNET was found to have an unclear risk of bias. A summary of the quality assessment is provided below in Table 9.

Table 9: Risk of bias assessment of GARNET trial using the CASP risk of bias tool for non-RCTs

Risk of bias	GARNET trial
Are the results of the study valid?	

Did the study address a clearly focussed issue?	Objective: To evaluate the antitumour activity of dostarlimab in patients with recurrent and advanced dMMR/MSI-H EC, in terms of ORR and DOR by BICR using RECIST v1.1
Yes/No/Unclear	YES
Was the cohort recruited in an acceptable way?	Patients were recruited from 117 sites in 9 countries as part of this multicentre, global clinical trial according to pre-defined eligibility criteria
Yes/No/Unclear	YES
Was the exposure accurately measured to minimise bias?	Standard, validated, objective measurements were evaluated including ORR, DOR, DCR, PFS
Yes/No/Unclear	YES
Was the outcome accurately measured to minimise bias?	Outcomes were assessed by BICR according to RECIST criteria
Yes/No/Unclear	YES
Have the authors identified all important confounding factors?	Predefined subgroup data cross some factors
Yes/No/Unclear	YES/PARTIAL
Have they taken account of the confounding factors in the design and/or analysis?	Predefined subgroup data cross some factors
Yes/No/Unclear	YES/PARTIAL
Was the follow-up of patients complete enough?	Follow-up was sufficiently recorded: The most common reason for treatment discontinuation was PD; Most of the study discontinuations were because of death
Yes/No/Unclear	YES
Was the follow-up of patients long enough?	Median OS was immature; however, the follow-up was long enough to determine the other outcomes
Yes/ No/Unclear	NO
What are the results?	
How precise are the results?	95% CIs were generally within a reasonable range; some of the smaller subgroups are large intervals
Yes/No/Unclear	YES/PARTIAL
Do you believe the results?	Evaluated by BICR under clinical trial conditions
Yes/ No/Unclear	YES
Will the results help locally?	
Can the results be applied to the local population?	A global multicentre study with generally good generalisability; however, the majority of patients were white so may not be relevant to some populations
Yes/No/Unclear	YES/PARTIAL
Do the results of this study fit with other available evidence?	No other published studies for dostarlimab in EC
Yes/No/Unclear	UNCLEAR
What are the implications of this study for practice?	Clinical trial evidence for dostarlimab in EC; however, not an RCT and therefore the extent of benefit versus other treatments is not clear
Yes/No/Unclear	UNCLEAR

Overall	Clinical trial evidence for dostarlimab in EC; however, not an RCT and therefore the extent of benefit versus other treatments is not clear
High/unclear/low	UNCLEAR

Abbreviations: BICR: blinded independent central review; CASP: Critical Appraisal Skills Programme; CIs: confidence intervals; DCR: disease control rate; dMMR: mismatch repair deficient; DOR: duration of response; EC: endometrial cancer; MSI-H: microsatellite instability-high; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; RCT: randomised controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours.
Source: GSK Data on File.[13]

B.2.3.2 Current clinical management (UK RWE study)

To mitigate the impact of the paucity of data identified for comparator therapies in the clinical SLR (see Appendix D), a GSK-initiated RWE study was conducted to describe the characteristics, treatments and outcomes for patients diagnosed with recurrent or advanced EC in the UK.

The study identified a large population of patients (N=[redacted]), who were closely aligned with those in GARNET, and for whom detailed data on baseline characteristics, prognostic variables and survival outcomes were available. The UK RWE study provides a real-world representation of current clinical management in this difficult-to-treat patient population where there is a paucity of relevant data in the literature. Accordingly, this UK RWE study serves as the primary comparative efficacy evidence in this submission and informs the base case cost-effectiveness analysis. Full details of the UK RWE study are presented in Section B.2.3.2 and B.2.4.5. To explore the impact of any potential differences in patient populations, an ITC was conducted between GARNET and the UK RWE study for OS, and details of this analysis are presented in Section B.2.7.1.

The methodology of the UK RWE study is presented below.

B.2.3.2.1 Summary of study methodology

Study design

The UK RWE study used routine, linked patient-level UK health data available through the NCRAS, which combines linked data from the Hospital Episode Statistics (HES), SACT, National Radiotherapy Dataset (RTDS), Cancer Outcomes and Services Dataset (COSD) and Office for National Statistics (ONS) mortality data. Data were collected for patients diagnosed between 1st January 2013 and 31st December 2018, with data extraction until 30th September 2020.

A brief summary of the eligibility criteria of the study is provided in the sections below, with further details provided in Appendix O.1.

Initial inclusion and exclusion criteria to identify patients with EC

Initially, a series of inclusion and exclusion criteria were defined in order to narrow down the total number of patients available to only adult patients with EC for whom sufficient data were available (date of diagnosis, stage at diagnosis and age at diagnosis). These initial inclusion and exclusion criteria are detailed in Table 10.

Table 10: Initial inclusion and exclusion criteria of the UK RWE study to identify patients with EC

Inclusion criteria	Exclusion criteria
• Resident in England on the date of diagnosis. • At least one incident primary diagnosis of advanced[a] or recurrent[b] EC between 01/01/2013 and 31/12/2018.	• Diagnoses via death certificate only (as patients would be ineligible for survival analyses). • No recorded date of diagnosis (as this would preclude the ability to select incident cases during the specified time window of the study). • No recorded stage at diagnosis such that advanced and recurrent disease cannot be reliably differentiated. • No recorded age at diagnosis.

Footnotes: [a] Advanced disease was defined as patients who were FIGO Stage III/IV at diagnosis. [b] Probable recurrence was defined as patients who were FIGO Stage I/II and received surgery, systemic anti-cancer therapy or radiation therapy and then had a treatment gap greater than 90 days, followed by treatment with any treatment. This assumption was validated as reasonable by UK clinical expert opinion.
Abbreviations: EC: endometrial cancer; FIGO: International Federation of Gynaecology and Obstetrics; RWE: real-world evidence.
Source: GSK Data on File.[13]

Inclusion and exclusion criteria to identify patients with recurrent or advanced EC

In addition to the general inclusion and exclusion criteria outlined above, an additional series of inclusion and exclusion criteria were then applied to define a cohort of patients with recurrent or advanced EC, as detailed in Table 11.

Table 11: Inclusion and exclusion criteria of the UK RWE study to identify patients with recurrent or advanced EC

Inclusion criteria	Exclusion criteria

• Patients with at least one diagnosis of C54 (malignant neoplasm of corpus uteri), excluding C542 (malignant neoplasm of myometrium), as dated between 01/01/2013 and 31/12/2018 inclusive, were included.
• Patients who presented with Stage I or Stage II EC were evaluated using the following criteria for the presence of recurrent disease:
  ○ Probable recurrence was defined as the first occurrence of a gap >90 days between any consecutive treatments (surgery, systemic therapy, radiation therapy including brachytherapy), with an index date for probable recurrent EC being equal to the date of treatment resumption following the >90-day gap.
  ○ To calculate gaps in treatment, treatment events were abstracted from their respective sources and sorted by ascending date. Further details on the algorithm used to derive the lines of therapy are presented in Appendix O.1.
  ○ Patients diagnosed at Stage I or Stage II and who did not experience a gap between treatments >90 days in direction were excluded.
• Patients presented with Stage III or Stage IV EC were classified with advanced EC, with an index date equal to the date of diagnosis.
• In any instance where a patient had multiple eligible EC diagnoses during the period of study entry (01/01/2013–31/12/2018), the patient entered the study according to the diagnosis with the earliest index date.
	• NA

Abbreviations: EC: endometrial cancer; NA: not applicable.
Source: GSK Data on File.[13]

Inclusion and exclusion criteria to identify patients for a GARNET-like cohort

The primary population considered in the comparative efficacy analysis (and the base case cost-

effectiveness analysis, described in Section B.3.2.1) is a smaller population of patients with recurrent or advanced EC who also fulfilled a further pre-defined set of eligibility criteria designed to identify a cohort of patients that were as closely matched as possible to the population of the GARNET trial. In order to be included in this 'GARNET-like cohort', patients additionally had to fulfil all of the inclusion and exclusion criteria listed in Table 12.

Table 12: Inclusion and exclusion criteria of the UK RWE study to identify patients for a GARNET-like cohort

Inclusion criteria	Exclusion criteria
• A diagnosis of recurrent or advanced EC, in line with the criteria in Table 11. • Patients must have received exactly one prior platinum doublet therapy for recurrent or advanced disease.	• Patients with any evidence of having received any anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy were excluded. • Patients with a histology of endometrial sarcoma and carcinosarcoma were excluded (the full list of histology classifications that were included and excluded can be found in Appendix O.1). • Patients with a record of another primary malignancy, except for non-melanoma skin cancer and carcinoma in situ cervix, were excluded. • Patients with an ECOG PS status ≥2 were excluded.

Abbreviations: EC: endometrial cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; PD-1: programmed cell death protein 1; PD-L1/L2: Programmed cell death ligand 1/2; RWE: real-world evidence.
Source: GSK Data on File[13].

An ECOG PS of ≤1 was a key inclusion criterion of the GARNET trial. However, patients with an ECOG PS of 'not recorded (NR)' were not excluded from the GARNET-like UK RWE cohort, in order to retain a larger sample size of patients, and to allow for a longer follow-up of data. It is likely that only a small minority of patients would have had an ECOG PS >1 if the PS of all patients had been known, given that the number of patients with an ECOG PS >1 only accounted for a small proportion of the overall RWE cohort of patients with recurrent or advanced EC (N=[redacted] [redacted%]). Furthermore, the NCRAS dataset does not provide details on why patients were classified with an ECOG PS of NR, and therefore excluding this group of patients could have introduced an unknown bias. However, in order to investigate the impact of not excluding patients with an ECOG PS of NR, a sensitivity analysis was conducted on a restricted cohort of patients, including only patients with a known ECOG PS of 0 or 1. This cohort is referred to as the 'GARNET-like ECOG PS ≤1' cohort; baseline characteristics and efficacy outcomes for this group of patients are detailed in Appendix O.2.

One limitation of the UK RWE study is that the dMMR/MSI-H biomarker is not recorded in the NCRAS database, and therefore, could not be used as an inclusion criterion for the UK RWE GARNET-like cohort. However, the impact of this is likely to be minimal. An SLR conducted by GSK found that there is no evidence that MSI-H or dMMR biomarker status has any prognostic or predictive value for efficacy and survival outcomes (including recurrence, relapse-free survival, PFS and OS) among patients with advanced or recurrent EC receiving non-anti-PD-(L)1 therapy.[62]

Patients with any evidence of receiving anti-PD-(L)1 therapy were excluded from the UK RWE GARNET-like population. As such, the survival outcomes for patients in the UK RWE study receiving current clinical management would not be expected to be significantly different for patients who were classified as dMMR/MSI-H, compared to the overall UK RWE GARNET-like population.

Study outcomes

Treatment use

The proportion of patients that had previously received surgical resection, systemic anti-cancer therapy or radiation therapy was recorded. The first occurrence of a doublet platinum regimen was identified by the delivery of cisplatin or carboplatin in combination with one other chemotherapy drug, and the distribution of distinct regimens occurring before and after the first doublet platinum regimen was then reported.

Durations of lines of therapy were calculated as the difference in days between the start (the initiation of the earliest selected regimen within the line) and end dates (the last known cycle or administration within a line) of a derived line.

Following the identification of the first doublet platinum therapy administration, an algorithm was applied to capture changes in therapy and breakdown of systemic regimens by derived line of therapy.[13] The algorithm has been applied on other studies and has been found to be generalisable to a range of solid tumours.[14,15] The detailed algorithm can be found in Appendix O.1.

Within the lines of therapy derived for each patient, distinct regimens and drug classes were flagged by line of therapy and patient counts were reported. In line with GARNET, hormone therapy (where identified) did not count towards prior lines of therapy where recorded.

Clinical outcomes

The key clinical outcomes sought in the study are listed below:

- **Baseline characteristics and patient demographics**: A range of key characteristics were collected, including: age, ethnicity, ECOG PS, stage at diagnosis, histology at diagnosis and Charlson comorbidity score.
- **OS from 2L:** OS was defined as the time from the initiation of 2L therapy (i.e. index date equal to start date of 2L therapy) until failure (all-cause death). This output was necessarily restricted to patients with derived lines of therapy via data available through the SACT.
- **TTNT from 2L:** As progression is not recorded within the NCRAS database, time to next therapy (TTNT) was used as a proxy for PFS. TTNT is a common proxy endpoint for PFS and this approach was validated by UK clinical experts. TTNT was defined as the time from the start of line of therapy until failure (the earliest of all-cause death or the start of a new line of treatment). Patients lost to follow-up or still in same line of treatment at the end of the study period were censored. This output was necessarily restricted to patients with derived lines of therapy via data available through SACT.
- **Time to treatment discontinuation (TTD) from 2L**: Treatment discontinuation was defined as the first of death or the date of any drug administration that is followed by a gap of >90 days.

Patient numbers

A summary of the patient numbers in the UK RWE study is provided in Figure 8. The incident 2L GARNET-like patient cohort (n=[redacted]) captures patients with recurrent or advanced EC that are treated with their subsequent line of therapy following their first line of platinum-based doublet

chemotherapy. This is also the point in the treatment pathway where patients would first be eligible for treatment with dostarlimab. Thus, this is the cohort of patients relevant to the decision problem.

Figure 8: Patients included in the UK RWE study

Abbreviations: 2L: second-line; EC: endometrial cancer; RWE: real-world evidence.

B.2.3.2.2 Baseline characteristics

Patient demographics and clinical characteristics

Patients in the GARNET-like RWE cohort had a mean age of [redacted] years. The majority of patients had an ECOG PS status of NR at the time of registry diagnosis ([redacted]%); [redacted]% and [redacted]% had an ECOG PS status of 0 and 1, respectively. [redacted] of the patients had received exactly one line of prior anti-cancer treatment following a diagnosis of recurrent or advanced EC, as outlined in the UK RWE study inclusion criteria.

Baseline patient demographics and clinical characteristics of patients in the GARNET-like UK RWE study cohort are presented in Table 13.

Table 13: Patient demographics and clinical characteristics in the GARNET-like UK RWE study cohort

Characteristic	GARNET-like RWE cohort ([redacted])
Mean age, years (STD)	[redacted]
Median age, years (range)	[redacted]
Age group, n (%)	
<65 years	[redacted]
65 to <75 years	[redacted]
≥75 years	[redacted]
Race, n (%)	
White	[redacted]
Black	[redacted]
Asian	[redacted]
Other[a]	[redacted]
Unknown[b]	[redacted]
ECOG PS at the time of registry diagnosis, n (%)[c]	
0	[redacted]
1	[redacted]
Not recorded	[redacted]
Histology at diagnosis, n (%)	

Carcinosarcoma	[redacted]
Clear cell carcinoma	[redacted]
Dedifferentiated/Undifferentiated carcinoma	[redacted]
Endometrioid	[redacted]
Mesonephroma	[redacted]
Mixed carcinoma	[redacted]
Mucinous	[redacted]
Neuroendocrine	[redacted]
Non-specific	[redacted]
Non-specific carcinoma	[redacted]
Sarcoma	[redacted]
Serous	[redacted]
Squamous	[redacted]
FIGO stage at the time of registry diagnosis, n (%)	
I	[redacted]
II	[redacted]
III	[redacted]
IV	[redacted]
Unknown	[redacted]
Grade of disease at diagnosis, n (%)	
Grade 1	[redacted]
Grade 2	[redacted]
Grade 3	[redacted]
Grade 4	[redacted]
Not assessable	[redacted]
Missing	[redacted]
Prior anticancer treatment, n (%)	
Any prior anti-cancer treatment	[redacted]
Prior surgery	[redacted]
Number of prior lines of therapy post advanced/recurrent diagnosis, n (%)	
1	[redacted]
2	[redacted]
3	[redacted]
≥4	[redacted]

Footnotes: [a] Includes American Indian or Alaska Native. [b] Includes Not reported.
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynaecology and Obstetrics; ITT: intention-to-treat; RWE: real-world evidence; STD: standard deviation.
Source: GSK Data on File.[13]

Most common chemotherapy regimens

Table 14 details the most common chemotherapy regimens received by patients with recurrent or advanced EC following their initial line of platinum-based chemotherapy derived from the UK RWE study. Overall, patients received a wide range of different regimens, with the most common regimens including carboplatin plus paclitaxel ([redacted]%), paclitaxel monotherapy ([redacted]%) and carboplatin plus PLD ([redacted]%).[13]

The wide range of different treatment regimens, including comparators outside of those included in the NICE final scope, demonstrates the clear lack of consensus around what which treatments represent the best options for the management of patients with recurrent or advanced EC who have progressed on or after a platinum-containing regimen in the UK.

Table 14: Most common chemotherapy regimens received by patients in the UK RWE study GARNET-like cohort

Chemotherapy regimen	Number of patients who received a regimen after their first doublet platinum regimen, n (%) (N=[redacted]) ([redacted]%)
Carboplatin plus paclitaxel	[redacted]
Paclitaxel monotherapy	[redacted]
Carboplatin plus PLD	[redacted]
PLD monotherapy	[redacted]
Carboplatin monotherapy	[redacted]
Cisplatin plus doxorubicin	[redacted]
Carboplatin plus gemcitabine	[redacted]
Carboplatin plus doxorubicin	[redacted]
Doxorubicin	[redacted]
Cisplatin	[redacted]
Carboplatin plus gemcitabine	[redacted]
Carboplatin plus doxorubicin	[redacted]
Carboplatin plus docetaxel	[redacted]
Carboplatin plus epirubicin	[redacted]
Cisplatin plus etoposide	[redacted]
Bevacizumab plus carboplatin plus paclitaxel	[redacted]
Carboplatin plus etoposide	[redacted]
Cisplatin plus cyclophosphamide plus doxorubicin	[redacted]
Bevacizumab	[redacted]
Cisplatin plus paclitaxel	[redacted]
Gemcitabine	[redacted]
Capecitabine plus oxaliplatin	[redacted]
Cisplatin plus gemcitabine	[redacted]
Cyclophosphamide plus doxorubicin plus vincristine	[redacted]

Carboplatin plus PLD plus paclitaxel	[redacted]
Niraparib	[redacted]
Topotecan	[redacted]

Footnotes: Data for the GARNET-like ECOG ≤1 cohort can be found in Appendix O.2.
Abbreviations: EC: endometrial cancer; PLD: pegylated liposomal doxorubicin; RWE: real-world evidence.
Source: GSK Data on File.[13]

B.2.4 Clinical effectiveness results from GARNET and the UK RWE study

The following sections present the clinical effectiveness results from GARNET and the UK RWE study. A descriptive comparison of key outcomes between dostarlimab and current clinical management, which includes naïve comparisons between both evidence from the UK RWE study and the literature is also presented.

B.2.4.1 Baseline characteristics (GARNET versus UK RWE study)

The patient demographics and clinical characteristics of the UK RWE study GARNET-like cohort and the GARNET ITT population are presented in Table 15, demonstrating broad similarity between the two patient groups. Patients in the GARNET ITT population were slightly younger than patients in the GARNET-like RWE cohort ([redacted] and [redacted] years respectively).

A greater number of patients were diagnosed with FIGO stage III and IV EC in the GARNET-like UK RWE study cohort ([redacted]% and [redacted]%, respectively) compared to patients in the GARNET ITT population ([redacted]% and [redacted]%, respectively). It is important to note that stage was recorded at the time of diagnosis in the UK RWE study, while the most recent stage at the time of study entry was recorded for patients in GARNET, which may account for this discrepancy.

More patients were diagnosed with ECOG PS 1 in the GARNET ITT population ([redacted]% of patients) recorded compared to patients in the GARNET-like UK RWE study cohort ([redacted]%). It is important to note however that ECOG PS is not directly comparable; ECOG PS was recorded at the time of diagnosis in the UK RWE study, while the most recent ECOG PS at the time of study entry was recorded for patients in GARNET, which may account for this discrepancy.

Table 15: Patient demographics and clinical characteristics in the GARNET-like UK RWE study cohort and ITT population of the GARNET trial

Characteristic	GARNET-like RWE cohort (N=[redacted])	GARNET ITT population (N=129)
Mean age, years (STD)	[redacted]	[redacted]
Median age, years (range)	[redacted]	[redacted]
Age group, n (%)		
<65 years	[redacted]	[redacted]
65 to <75 years	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black	[redacted]	[redacted]

Asian	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]
Unknown[b]	[redacted]	[redacted]
Most recent ECOG PS at registry diagnosis (UK RWE study) or study entry (GARNET), n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Not recorded	[redacted]	[redacted]
Histology at diagnosis, n (%)		
Endometrioid carcinoma type I	[redacted]	[redacted]
Endometrial carcinoma type II	[redacted]	[redacted]
Endometrioid	[redacted]	[redacted]
Clear cell carcinoma	[redacted]	[redacted]
Dedifferentiated/undifferentiated carcinoma	[redacted]	[redacted]
Histology unknown at time of diagnosis	[redacted]	[redacted]
Mixed carcinoma	[redacted]	[redacted]
Mucinous	[redacted]	[redacted]
Neuroendocrine	[redacted]	[redacted]
Non-specific	[redacted]	[redacted]
Non-specific carcinoma	[redacted]	[redacted]
Other	[redacted]	[redacted]
Serous carcinoma	[redacted]	[redacted]
Squamous carcinoma	[redacted]	[redacted]
Undifferentiated carcinoma	[redacted]	[redacted]
Unspecified	[redacted]	[redacted]
Most recent FIGO stage at diagnosis, n (%)[c]		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Grade of disease at diagnosis, n (%)		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Prior anticancer treatment, n (%)		
Any prior anti-cancer treatment	[redacted]	[redacted]
Prior surgery	[redacted]	[redacted]

Number of prior lines of therapy post advanced/recurrent diagnosis, n (%)		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
≥4	[redacted]	[redacted]

Footnotes: [a] Includes American Indian or Alaska Native. [b] Includes Not reported. [c] For the RWE study this is at registry diagnosis.
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynaecology and Obstetrics; ITT: intention-to-treat; RWE: real-world evidence; STD: standard deviation.
Source: GSK Data on File.[13]

B.2.4.2 Objective response rate (ORR)

The primary efficacy endpoint results of GARNET, in terms of ORR and DOR, are available for the efficacy population (N=[redacted]) only. According to the study protocol, only patients with at least 24 weeks of tumour assessment were eligible for ORR and DOR analyses; all patients with at least 24 weeks of tumour assessment at the time of IA2 (Data cut off [DCO] 1st March 2020) were included in the efficacy population.

Other efficacy endpoints, including PFS and OS, were analysed for both the efficacy population (N=[redacted]) and the ITT population (N=129) and are presented from Section B.2.6.2 onwards.

B.2.4.2.1 Dostarlimab (GARNET)

Dostarlimab demonstrated a robust and clinically meaningful ORR; [redacted]% of patients ([redacted]) achieved a complete or partial response when treated with dostarlimab, with [redacted]% of patients ([redacted]) experiencing a complete response (CR).

In the efficacy population (N=[redacted]), the ORR (measured as the proportion of patients who achieved a BOR of CR or partial response [PR] to treatment), was [redacted]% (n=[redacted]; 95% CI: [redacted]%, [redacted]%). In total, [redacted] patients ([redacted]%) achieved a CR, and [redacted] patients ([redacted]%) achieved a PR to treatment (Table 16).

A secondary efficacy endpoint in GARNET was DCR, which included patients achieving a BOR of CR or PR as well as patients with a BOR of stable disease (SD). A BOR of SD was observed in [redacted] patients ([redacted]%), resulting in a DCR of [redacted]% (n=[redacted]; 95% CI: [redacted]%, [redacted]%).

A detailed overview of the BOR to dostarlimab and the ORR in GARNET is presented in Table 16.

Table 16: Summary of the BOR to dostarlimab by RECIST v1.1 in GARNET (efficacy population) (BICR)

Response rate	Efficacy population (N=[redacted])
BOR by RECIST v1.1, n (%)	
CR	[redacted]
PR	[redacted]
SD	[redacted]
PD	[redacted]
NE	[redacted]

Not done	[redacted]
Confirmed ORR by RECIST v1.1	
n (%)[a]	[redacted]
95% CI[b]	[redacted]
Response ongoing[c]	[redacted]
DCR by RECIST v1.1, n (%)	[redacted]
95% CI[a]	[redacted]

Footnotes: [a] ORR was defined as the percentage of patients with a RECIST v1.1-confirmed CR or PR. DCR was defined as the percentage of patients with a RECIST v1.1-confirmed PR, confirmed CR, or SD. Response assessments were based on BICR. [b] Exact 2-sided 95% CI for the binomial proportion. [c] All responders who have not yet died or progressed (including clinical progression); the denominator for the percentage is the number of responders.
Abbreviations: BICR: blinded independent central review; BOR: best overall response; CI: confidence interval; CR: complete response; DCR: disease control rate; dMMR: mismatch repair-deficient; EC: endometrial cancer; MSI-H: microsatellite instability-high; NE: not evaluable; ORR: objective response rate; PD: progressive disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease.
Source: GSK Data on File.[13]

B.2.4.2.2 Dostarlimab versus current clinical management

ORR data were not collected in the UK RWE study for current clinical management. However, the response rates observed in GARNET are striking when compared to studies identified from the clinical SLR (detailed in Appendix D). ESMO guidelines highlight that for patients with EC recurring after first-line chemotherapy, only paclitaxel has consistently shown a response rate >20 (less than half the ORR achieved by dostarlimab).[47] Notably, the studies reporting ORRs for paclitaxel, such as Lincoln *et al.* (2003), which report an ORR for paclitaxel monotherapy of 27.3%, predate the use of paclitaxel as a first-line treatment for patients with recurrent or advanced EC.[49] It is therefore unlikely that similarly high ORRs would be observed for paclitaxel monotherapy in current clinical practice.

Accordingly, in more recent studies, McMeekin *et al.* (2015)[6] reports an ORR of 15.7% for patients receiving either paclitaxel or doxorubicin monotherapy (N=223); there were no patients that experienced a CR. For patients receiving doxorubicin monotherapy (N=225), the ZoptEC study reported an even lower ORR of 14.1%, with only 2.0% of patients experiencing a CR. The results for the comparator arm of the recently conducted KEYNOTE 775 trial which included doxorubicin or paclitaxel monotherapy showed similar response rates, with an ORR of 14.7% and only 2.6% of patients experiencing a CR.[8-10, 63]

There were only two relevant studies including patients treated with carboplatin plus paclitaxel in the clinical SLR. Both of these were small, retrospective studies: Mazgani *et al.* (2008) (N=31) and Rubinstein *et al.* (2019) (N=20), which reported similar ORRs to GARNET, of 38.7% and 50.0%, respectively. [59, 60] However, these studies report only very limited information on patient characteristics, meaning that it is completely unknown whether these patients are similar to those in GARNET. In the absence of more detailed information from these studies, it is not possible to make any robust comparisons between dostarlimab and carboplatin plus paclitaxel with any certainty.

B.2.4.3 Duration of response (DOR)

B.2.4.3.1 Dostarlimab (GARNET)

The response to dostarlimab is durable – after a median follow-up of [redacted] months, [redacted]% of patients ([redacted]) were still experiencing an ongoing response at the IA2 DCO (1st March 2020). The probability of maintaining a response until Month 12 and Month 18 was estimated at [redacted]% and [redacted]%, respectively.

A summary of the DOR in GARNET is presented in Figure 9. At the time of IA2 (DCO 1st March 2020), [redacted]% of patients ([redacted]) treated with dostarlimab were still in response, after a median follow-up of [redacted] months. The median DOR was [redacted] (range: [redacted] to [redacted] months, where + indicates response is still ongoing) (Figure 9).

The probability of maintaining a response until Month 6, Month 12 and Month 18 was: [redacted]% (95% CI: [redacted], [redacted]), [redacted]% (95% CI: [redacted], [redacted]), and [redacted]% (95% CI: [redacted], [redacted]), respectively (calculated using KM estimation) (Table 17).

In comparison, only one study identified in the clinical SLR reported the median DOR; patients treated with paclitaxel monotherapy in Lincoln *et al.* (2003) experienced a median DOR of just 4.2 months.[49]

Figure 9: DOR (from time of first PR or CR) based on RECIST v1.1 in GARNET (efficacy population) (BICR)

Abbreviations: BICR: blinded independent central review; CR: complete response; dMMR: mismatch repair deficient; EC: endometrial cancer; PD: progressive disease; PR: partial response; RECIST v1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SD: stable disease.
Source: GSK Data on File.[13]

Table 17: KM analysis of DOR based on BICR in GARNET (efficacy population; patients with objective response)

DOR	Patients in the efficacy population with an objective response (N=[redacted])
DOR status, n (%)	
Events observed	[redacted]
Censored	[redacted]
Median duration of follow-up (months)	[redacted]
DOR (months)	
Min, Max	[redacted]
Quartile (95% CI)	
25%	[redacted]
50%	[redacted]
75%	[redacted]
Duration ≥6 months, n (%)	[redacted]
DOR distribution function (95% CI)	
Month 6	[redacted]
Month 12	[redacted]
Month 18	[redacted]

Footnotes: [a] 95% CIs were generated using the method of Brookmeyer and Crowley (1982).[64] [b] A "+" indicates that the patient's response is ongoing.
Abbreviations: BICR: blinded independent central review; CI: confidence interval; dMMR: mismatch repair-deficient; DOR: duration of response; EC: endometrial cancer; KM: Kaplan-Meier; max: maximum; min: minimum; MSI-H: microsatellite instability high; NE: not evaluable; RECIST: Response Evaluation Criteria in Solid Tumours.
Source: GSK Data on File.[13]

B.2.4.3.2 Dostarlimab versus current clinical management

DOR data were not collected in the UK RWE study for current clinical management. The only study in the clinical SLR reporting DOR was Lincoln *et al*. (2003), which reported a median DOR of 4.2 months for patients receiving paclitaxel monotherapy (N=44).[49]

B.2.4.4 Change in target lesion size

B.2.4.4.1 Dostarlimab (GARNET)

The [redacted] of patients who experienced a response to treatment with dostarlimab experienced more than a [redacted] in tumour size, in comparison to baseline.

A waterfall plot of the by-patient maximum percentage change in tumour size by RECIST v1.1 for the efficacy population in GARNET is presented in Figure 10. The maximum percentage change in target lesions from baseline is indicated by bar length. The waterfall plot demonstrates that the majority of patients who experienced a response to treatment with dostarlimab experienced a clinically meaningful [redacted] reduction in tumour size in comparison to baseline.

Figure 10: Waterfall plot of the maximum percentage change in target lesions compared with baseline measurements based on BICR per RECIST v1.1 in GARNET (efficacy population)

Footnotes: Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. Horizontal reference ranges are defined by -30 for PR.
Abbreviations: BICR: blinded independent central review; CR: complete response; dMMR: mismatch repair-deficient; EC: endometrial cancer; NE: not evaluable; PD: disease progression; PR: partial response; RECIST v1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SD: stable disease.
Source: GSK Data on File.[54]

B.2.4.4.2 Dostarlimab versus current clinical management

Changes in target lesion size data were not collected in the UK RWE study for current clinical management, or reported in any of the studies included for comparators in the clinical SLR. It is therefore not possible to make any comparisons in terms of changes in target lesion size between dostarlimab and current clinical management.

B.2.4.5 Progression-free survival (PFS)

B.2.4.5.1 Dostarlimab (GARNET)

Overall, [redacted]% and [redacted]% of patients in the ITT population were progression free at Month 12 and Month 24, respectively. The [redacted], and the PFS curve subsequently plateaued, suggesting the potential for a long-term PFS benefit with dostarlimab.

In the ITT population of GARNET (N=129), [redacted] PFS events were observed, with [redacted]. Following this, a clear plateau was observed. At Month 6, [redacted]% of patients in GARNET had not experienced disease progression or death. Very few patients then experienced disease progression or death in the next six months, with [redacted]% of patients in GARNET remaining progression-free at Month 12. Patients treated with dostarlimab continued to experience a long-term PFS benefit through to Month 18 and Month 24, with [redacted]% and [redacted]% of patients remaining free of disease progression of death.

Due to the plateauing of the PFS KM curve, when approximately [redacted]% of patients had experienced

disease progression or death, the median PFS of [redacted] months is highly uncertain, and associated with very wide CIs (95% CI: [redacted], [redacted]). As such, the median PFS must be interpreted with caution, and [redacted]. This is illustrated in Section B.2.7.1, where rounding the individual PFS estimates for each patient to one decimal place (versus two decimal places) changes the median PFS from [redacted] months to [redacted] months.

However, [redacted], the overall shape of the KM curve and the presence of a plateau suggests patients who remain progression-free may experience a long-term PFS benefit from dostarlimab treatment through to Month 18 and Month 24, with [redacted]% and [redacted]% of patients remaining free of disease progression of death.

A similar trend was observed in the efficacy population (N=[redacted]). The majority of the [redacted] PFS events occurred within the first six months, with [redacted]% of patients remaining progression-free at Month 6. A similar plateau was then observed, with [redacted]% of patients remaining progression-free at Month 12 and [redacted]% at Month 24.

It is also important to note that because dostarlimab is an I-O therapy, the conventional RECIST criteria may not be an adequate measure to monitor response rates and disease progression; successful treatment response following I-O therapies manifests differently, including delayed response, transient tumour enlargement followed by shrinkage, stable size, or initial presence of new lesions followed by stability or response.[65, 66] Immune-related PFS (irPFS; presented in Section B.2.4.7) may therefore suggest that the PFS results presented below, according to the traditional RECIST v1.1, may actually underestimate the true PFS benefit of dostarlimab.

Table 18 presents further details of PFS across both the efficacy and ITT populations, while PFS KM curves are presented in Figure 11.

Table 18: KM analysis of PFS from GARNET (efficacy population and ITT population) (BICR)

PFS	Efficacy population (N=[redacted])	ITT population (N=129)
PFS[a] status, n (%)		
Events observed	[redacted]	[redacted]
Censored	[redacted]	[redacted]
PFS by quartile (95% CI[a]), months		
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]
PFS distribution function (95% CI)		
Month 6	[redacted]	[redacted]
Month 9	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	[redacted]	[redacted]

Footnotes: [a] PFS was defined as the time from the first dose of treatment to disease progression or death, whichever occurred first. [b] Landmark survival estimates at Month 18 and Month 24 were taken from the KM data included in the dostarlimab cost-effectiveness model, and as such, associated confidence intervals are not

available.
Abbreviations: BICR: blinded independent central review; CI: confidence interval; EC: endometrial cancer; ITT: intention-to-treat; KM: Kaplan-Meier; NR: not reachable; PFS: progression-free survival.
Source: GSK Data on File.[13]

Figure 11: PFS KM curves from GARNET (efficacy population and ITT population) (BICR)

Abbreviations: BICR: Blinded Independent Central Review; ITT: intention-to-treat; KM: Kaplan-Meier; MSI-H: microsatellite instability-high; PFS: progression-free survival.
Source: GSK Data on File.[13]

B.2.4.5.2 Dostarlimab versus current clinical management

UK RWE study

Dostarlimab markedly improves PFS versus current clinical management; only [redacted]% and [redacted]% of a population of GARNET-like patients in the UK RWE study were progression-free at Month 12 and 24, compared with [redacted]% and [redacted]% in the GARNET ITT population, respectively.

Considering a naïve comparison, patients receiving dostarlimab had a substantially reduced risk of disease progression or death, relative to patients receiving current clinical management based on the UK RWE study (which used TTNT as a proxy for PFS).

In the UK RWE study 'GARNET-like' cohort, [redacted]% of patients had not experienced disease progression or death at Month 6, dropping drastically to [redacted]% of patients who remained progression-free at Month 12 (Figure 12). In stark contrast, [redacted]% of patients treated with dostarlimab in the GARNET trial were progression-free at [redacted]; notably the PFS curve then plateaued. Very few patients treated with dostarlimab experienced disease progression or death over the next six months, with [redacted]% of patients remaining progression-free at Month 12.

Patients treated with dostarlimab in the GARNET trial then experienced a sustained, long-term PFS benefit through to Month 24, with [redacted]% of patients remaining progression-free. However,

there is almost no evidence for a sustained PFS benefit for patients receiving current clinical management in the UK RWE study 'GARNET-like' cohort, with only a small minority of patients ([redacted]%) remaining progression-free at Month 24.[13]

Notably, these results likely overestimate the true PFS for patients in the UK RWE study 'GARNET-like' cohort. The UK RWE study used TTNT as a proxy for PFS, and in reality, it is likely that patients would experience a delay between disease progression and the initiation of their next line of treatment. As such, the true PFS for these patients is likely to be lower than the estimates based on TTNT.[13]

The naïve PFS comparison between GARNET and the UK RWE study is summarised in Table 19.

Figure 12: TTNT as a proxy for PFS for patients with recurrent or advanced EC that have progressed on or after platinum-based chemotherapy receiving current clinical management (UK RWE GARNET-like cohort)

Footnotes: PFS for patients in the GARNET-like ECOG PS ≤1 cohort of the UK RWE study is detailed in Appendix O.2.
Abbreviations: CI: confidence interval; EC: endometrial cancer; PFS: progression-free survival; RWE: real-world evidence; TNTT: time to next treatment.
Source: GSK Data on File.[13]

Table 19: Naïve PFS comparison for patients with recurrent or advanced EC that have progressed on or after platinum-based chemotherapy (UK RWE study versus GARNET)

	GARNET-like UK RWE study (current clinical management) (N=[redacted])	GARNET ITT population (dostarlimab) (N=129)
Median PFS (months) (95% CI)	[redacted]	[redacted]

PFS distribution function (95% CI)		
Month 6	[redacted]	[redacted]
Month 9	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18[a]	[redacted]	[redacted]
Month 24[a]	[redacted]	[redacted]

Footnotes: TTNT was used as a proxy for PFS in the UK RWE study. PFS for patients in the GARNET-like ECOG PS ≤1 cohort of the UK RWE study is detailed in Appendix O.2. [a] Landmark survival estimates at Month 18 and Month 24 for GARNET were taken from the KM data included in the dostarlimab cost-effectiveness model, and as such, associated confidence intervals are not available
Abbreviations: CI: confidence interval; EC: endometrial cancer; ITT: intention-to-treat; PFS: progression-free survival; RWE: real-world evidence.
Source: GSK Data on File.[13]

Published literature

The sustained benefit in terms of PFS for patients treated with dostarlimab is a critical difference versus published PFS curves for the comparator chemotherapies identified in the clinical SLR. While other studies report comparable or increased median PFS estimates versus GARNET, there is almost no evidence of a plateau or long-term PFS benefit in these studies. Patients treated with doxorubicin monotherapy in the ZoptEC study had a median PFS of 4.7 months (95% CI: 4.1, 6.6), but very few patients were progression-free by Month 24.[8-10] Rubinstein *et al.* (2019) and Mazgani *et al.* (2008) report higher median PFS estimates of 10 months (95% CI: 2.0, 47.0) and 8 months (95% CI: 5.0, 13.0), respectively, for patients receiving carboplatin plus paclitaxel.[59, 60] However, 5.2% and 14.7% of patients in these studies were progression-free at Month 24, compared to [redacted]% of patients in GARNET.

B.2.4.6 Overall survival (OS)

B.2.4.6.1 Dostarlimab (GARNET)

A remarkable [redacted]% of patients were alive at Month 12 after treatment with dostarlimab. Patients experienced a sustained survival benefit – [redacted] of the patients in GARNET ([redacted]%) were still alive by Month 24.

In the ITT population of GARNET (N=129), [redacted] OS events were observed at the time of the IA2 DCO (1st March 2020). Patients treated with dostarlimab experienced a clear OS benefit relative to patients receiving current clinical management in UK clinical practice. At Month 12, a remarkable [redacted]% of patients were still alive. While the OS data are still immature, a clear plateau is observed from approximately [redacted] (Figure 13), with [redacted]% of patients still alive at Month 18, and [redacted]% of patients still alive at Month 24.

The median OS has [redacted] at the time of the IA2 DCO. However, it is reasonable to assume that the true median OS estimate is, at a minimum, equal to the lower confidence bound of [redacted] months.

The efficacy population showed a similar trend: [redacted] OS events were observed, with [redacted]% of patients alive at Month 12, and [redacted]% of patients alive at Month 24. The median OS was also [redacted] at the time of the IA2 DCO.

Table 20 presents further details of OS across both the efficacy and ITT populations, while OS

KM curves are presented in Figure 13.

Table 20: KM analysis of OS from GARNET (efficacy population and ITT population)

OS	Efficacy population (N=[redacted])	ITT population (N=129)
OS[a] status, n (%)		
Events observed	[redacted]	[redacted]
Censored	[redacted]	[redacted]
OS by quartile (95% CI[a]), months		
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]
OS distribution function (95% CI)		
Month 6	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18	[redacted][c]	[redacted][c]
Month 24	[redacted][c]	[redacted][c]

Footnotes: [a] OS was defined as the time from the date of the first dose of study treatment to the date of death by any cause. [b] 95% CIs were generated using the method of Brookmeyer and Crowley (1982).[64] [c] Landmark survival estimates at Month 18 and Month 24 were taken from the KM data included in the dostarlimab cost-effectiveness model, and as such, associated confidence intervals are not available.
Abbreviations: CI: confidence interval; KM: Kaplan-Meier; NR: not reached; OS: overall survival.
Source: GSK Data on File.[13]

Figure 13: OS KM curves from GARNET (efficacy population and ITT population)

[redacted]

Abbreviations: KM: Kaplan-Meier; ITT: intention-to-treat; OS: overall survival.
Source: GSK Data on File.[13]

B.2.4.6.2 Dostarlimab versus current clinical management

UK RWE study

Only one in five ([redacted]%) GARNET-like patients initiating further chemotherapy in the UK RWE cohort were still alive at Month 24 – [redacted] the percentage of patients treated with dostarlimab in GARNET who were still alive ([redacted]%) at Month 24

The naïve OS comparison between GARNET and the UK RWE study demonstrates that patients treated with dostarlimab experienced a marked reduction to the risk of death versus patients treated with current clinical management in the UK.

In the UK RWE study 'GARNET-like' cohort, [redacted]% of patients were still alive at Month 12; by Month 24, just [redacted]% were still alive (Figure 14). The comparison with GARNET is clear and conclusive: [redacted]% of patients in GARNET were still alive at Month 12, and [redacted]% of patients were still alive at Month 24, [redacted] the percentage of patients still alive that received current clinical management, highlighting the dire prognosis faced by patients in current clinical practice.

Figure 14: OS for patients with recurrent or advanced EC that has progressed on or after platinum-based chemotherapy receiving current clinical management (UK RWE GARNET-like cohort)

Footnotes: OS for patients in the GARNET-like ECOG PS ≤1 cohort of the UK RWE study is detailed in Appendix O.2.
Abbreviations: CI: confidence interval; EC: endometrial cancer; OS: overall survival; RWE: real-world evidence.
Source: GSK Data on File.[13]

The naïve OS comparison between GARNET and the UK RWE study is summarised in Table 21.

Table 21: Naïve OS comparison for patients with recurrent or advanced EC that has progressed on or after platinum-based chemotherapy (UK RWE study versus GARNET)

	GARNET-like UK RWE study (current clinical management) (N=[redacted])	GARNET ITT population (dostarlimab) (N=129)
Median OS (months) (95% CI)	[redacted]	[redacted]
OS distribution function (95% CI)		
Month 6	[redacted]	[redacted]
Month 9	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18[a]	[redacted]	[redacted]
Month 24[a]	[redacted]	[redacted]

Footnotes: OS for patients in the GARNET-like ECOG PS ≤1 cohort of the UK RWE study is detailed in Appendix O.2. [a] Landmark survival estimates at Month 18 and Month 24 for GARNET were taken from the KM data included in the dostarlimab cost-effectiveness model, and as such, associated confidence intervals are not available.
Abbreviations: CI: confidence interval; EC: endometrial cancer; ITT: intention-to-treat; OS: overall survival; RWE: real-world evidence.
Source: GSK Data on File.[13]

Published literature

Of the studies identified in the clinical SLR, patients receiving doxorubicin monotherapy in the ZoptEC study had a median OS of 10.8 months (95% CI: 9.8, 12.6), with 23.0% of patients alive at Month 24. Similarly, patients receiving paclitaxel or doxorubicin monotherapy in McMeekin *et al.* (2015) had a median OS of 12.3 months (95 CI: 10.7, 15.4), with just 29.4% of patients alive at Month 24.[6, 8-10] For patients treated with carboplatin plus paclitaxel, Mazgani *et al.* (2008) reported a median OS estimate of 15.0 months (95% CI: 9.1–30.4) (patients with an endometrioid histology), with 35.5% of patients alive at Month 24. Rubinstein *et al.* (2019) reported a median OS of 27.0 months (95% CI: 6.0, 117.0), with 59.5% of patients alive at Month 24.[59, 60]

B.2.4.7 Immune-related endpoints (dostarlimab only)

The primary analyses of response rates and PFS in GARNET were based on the conventional RECIST v1.1 criteria, which measure response by the reduction in tumour size following chemotherapy. However, these criteria are primarily designed to measure disease-progression following traditional cytotoxic chemotherapy. In contrast, successful treatment response following I-O therapies manifests differently, including delayed response, transient tumour enlargement followed by shrinkage, stable size, or initial presence of new lesions followed by stability or response.[65] Consequently, the conventional RECIST criteria may not be an adequate measure in monitoring response to these unique therapies.[65, 66]

The modified irRECIST provides an alternative measurement of endpoints that is able to more reliably account for the tumour response to I-O therapies. The primary difference between this measure and the conventional criteria is the introduction of an additional follow-up to confirm or withdraw ‘unconfirmed’ tumour progression after an initial increase in size.[66]

Consequently, the immune-related endpoints presented below may reflect a more representative assessment of the true benefit of dostarlimab. It is important to note that irRECIST was evaluated

by Investigator Assessment in GARNET, while the primary response rate analyses presented above were evaluated by BICR.

Immune-related progression-free survival (irPFS) data are presented below, while immune-related response rate endpoints are presented in Appendix N.2.

Immune-related progression-free survival (irPFS)

The irPFS results demonstrate a very similar trend to PFS assessed by conventional RECIST. A proportion of patients experienced disease progression very early (within the [redacted] of treatment), but then the survival curve begins to level off and plateau from approximately [redacted]. Additional details on irPFS are presented in Table 22, and the irPFS KM curve is presented in Figure 15.

In comparison to PFS assessed by conventional RECIST, a greater percentage of patients were alive at Month 6 ([redacted]%) and Month 12 ([redacted]%) by irRECIST, compared to the number of patients who were progression free in the efficacy population at the same time points ([redacted]% and [redacted]%). By the time the PFS curve completely plateaus, a remarkable [redacted]% of patients were progression-free at Month 24, slightly lower than the [redacted]% of patients who were progression-free by conventional RECIST at the same point. Despite the slight differences in these results, it is clear that regardless of how PFS is assessed, patients experience a clear and sustained benefit following treatment with dostarlimab.

Notably, the median irPFS is much higher, at [redacted] months (95% CI: [redacted], [redacted]), versus the median PFS estimate of [redacted] months (95% CI: [redacted], [redacted]) for the efficacy population per conventional RECIST. This is a drastic difference with similar numbers of PFS events observed between the two populations ([redacted] versus [redacted], respectively) and only small differences in the percentages of patients progression-free at Month 6 and Month 12.

Alongside the wide CIs associated with the median PFS estimates, this drastic difference in PFS serves to further highlight that, because of the plateau observed when approximately [redacted] of patients are progression-free, the median PFS is heavily influenced by just one or two patients who experienced a PFS event in this interim data cut across different populations, and therefore median PFS estimates (for PFS per conventional or irRECIST) do not represent a robust summary statistic to estimate the PFS benefit associated with dostarlimab.

Table 22: irPFS per irRECIST KM analysis in GARNET (immune-related efficacy population) (Investigator Assessment)

Variable	Immune-related efficacy population (N=[redacted])
irPFS[a] status, n (%)	
Events observed	[redacted]
Censored	[redacted]
Quartile (95% CI[b])	
25%	[redacted]
50%	[redacted]
75%	[redacted]
irPFS distribution function (95% CI)	
Month 6	[redacted]

Month 9	[redacted]
Month 12	[redacted]
Month 18[c]	[redacted]
Month 24[c]	[redacted]

Footnotes: [a] irPFS was defined as the time from the date of the first dose to the earlier date of assessment of irPD event or death by any cause in the absence of disease progression based on the time of irPD event per irRECIST. [b] CIs were generated using the method of Brookmeyer and Crowley (1982).[64] [c] Landmark survival estimates at Month 18 and Month 24 were taken from the KM curve and as such, associated confidence intervals are not available.
Abbreviations: CI: confidence interval; irPFS: immune-related progression-free-survival; irRECIST: immune-related Response Evaluation Criteria in Solid Tumors; KM: Kaplan-Meier; NR: not reachable.
Source: GSK Data on File.[13]

Figure 15: irPFS per irRECIST KM curve in GARNET (immune-related efficacy population) (Investigator Assessment)

[redacted]

Footnotes: Medians presented in months.
Abbreviations: CI: confidence interval; dMMR: DNA mismatch repair deficiency; EC: endometrial cancer; irPFS: immune-related progression-free survival; irPFS: immune-related Response Evaluation Criteria in Solid Tumors; KM: Kaplan-Meier; NR: not reported.
Source: GSK Data on File.[54]

B.2.4.8 Health-related quality of life (dostarlimab only)

Treatment with dostarlimab preserved patient-reported HRQoL from baseline. Key disease-related symptom subscales, such as pain and fatigue showed a positive trend of improvement throughout the study.

European Quality of Life (EQ) Visual Analogue Scale (VAS)

The EQ-5D-5L is a generic HRQoL questionnaire comprising of five dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[67] Each dimension has five levels of severity: no problems, slight problems, moderate problems, severe problems and extreme problems.[67] Tariffs are anchored at 1 for full health and 0 for health states

considered equivalent to death.[67] A summary of patient responses to each of the EQ-5D-5L subscales at each timepoint in the GARNET trial is presented in Appendix N.3.

The EQ-VAS assesses patients perceived overall health status on the day of scoring on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). The adjusted mean change from baseline in EQ-VAS is presented in Figure 16. At baseline, the mean EQ-VAS score was [redacted] (STD: [redacted]). Whilst the level of change fluctuated throughout the study duration, a general trend of improvement in EQ-VAS score was observed. At Week 12, the mean EQ-VAS score was [redacted] (STD: 18.0), demonstrating a mean improvement from baseline of [redacted] (STD: [redacted]). At Week 18, improvements in EQ-VAS score continued, with a mean score of [redacted] (STD: [redacted]), demonstrating a mean improvement from baseline of [redacted] (STD: [redacted]). At Week 42, the improvement remained the same, with a change from baseline of 4.0 (STD: [redacted]). Whilst a greater improvement in score was observed after end of treatment, the number of subjects at each visit was notably low.

Figure 16: Adjusted Mean Change from Baseline in EQ-VAS (GARNET efficacy population)

[redacted]

Footnotes: Adjusted mean and 95% CI are from mixed model repeated measures (MMRM) with week visit, and Eastern Cooperative Oncology Group (ECOG) status as factors and baseline score as continuous covariate as well as an unstructured covariance structure.
Abbreviations: EOT: end-of-treatment; EQ-VAS: EuroQol-visual analogue scale; PRO: patient reported outcome; SUVF: survival follow-up; WX: week X.
Source: GSK Data on File.[13]

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

The EORTC QLQ-C30 is an internationally validated HRQoL questionnaire for cancer. It contains five scales for functioning (physical, social, role, cognitive, and emotional functioning), eight symptom scales (fatigue, nausea/vomiting, pain, dyspnoea, sleep disturbances, appetite loss, constipation, and diarrhoea), financial impact, and an assessment for overall QoL. For the functioning scales and global QOL higher scores indicate better functioning; for the symptom scales, higher scores indicate increased symptom burden.[68]

EORTC QLQ-C30 data were available for [redacted] of the 129 patients in the ITT population of GARNET. The completion rate for the EORTC QLQ-C30 was consistent across domains, ranging from [redacted]% at baseline to [redacted]% at Cycle 7.

The global health/quality of life (QoL) change over time from Baseline and the mean scores over time demonstrated a clear improvement.

Figure 17: Mean change in Global Health Status/QOL from Baseline (GARNET ITT population)

Abbreviations: ITT: intention-to-treat; QoL: quality of life.
Source: GSK Data on File.[13]

Overall, the EORTC QLQ-C30 results showed that patients treated with dostarlimab reported that key disease-related symptom subscales, including pain and fatigue, improved or remained stable over time while on treatment. Both patient-reported pain and fatigue symptoms showed a downwards trend of improvement below baseline (reduced pain and fatigue symptoms), starting at Cycle 2 and Cycle 3, respectively.

Patients also reported an improvement in physical functioning over time while on treatment, with a positive trend of improvement (increased physical functioning) above baseline from Cycle 4, which then remained stable thereafter (Figure 18).

Figure 18: Pain, fatigue and physical functioning mean change from baseline (GARNET ITT population)

Abbreviations: CxDx: Cycle X Day X; ITT: intention-to-treat.
Source: GSK Data on File.[13]

For patients who experienced symptomatic adverse events (AEs) included in the symptom

scales of the EORTC QLQ-C30, including nausea, vomiting, constipation, diarrhoea, or tiredness, the majority remained stable or had improvement in these symptoms over the treatment course compared to their baseline. Only a minority of patients reported worsening in these AE symptoms including [redacted]% who reported single-category worsening and [redacted]% who reported 2- or 3-category worsening.

More detailed analyses of the change in symptomatic AEs in response from baseline are presented in Figure 19.

Figure 19: Symptomatic AE change in response from baseline (GARNET ITT population)

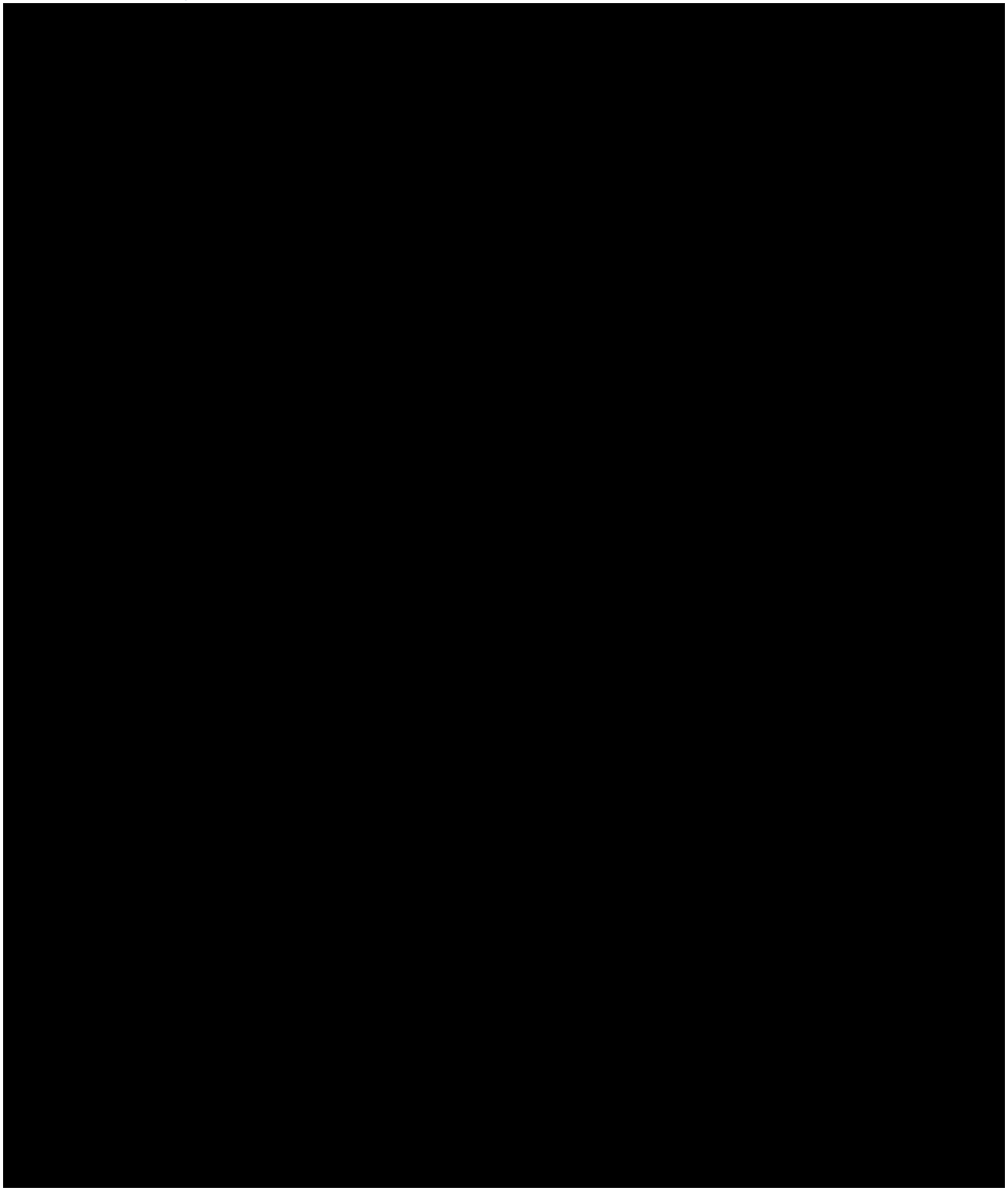
Abbreviations: AE: adverse event; CxDx: Cycle X Day X; ITT: intention-to-treat.
Source: GSK Data on File.[13]

B.2.5 Subgroup analysis (dostarlimab only)

Dostarlimab (GARNET)

Subgroup analyses for ORR in the efficacy population are presented in Figure 20. With the exception of the subgroup analysis by ECOG performance status, all categories of the subgroup analyses using this data cutoff date show overlapping 95% CIs with the overall population ORR. With the exception of the [redacted] patients for whom the most recent FIGO stage was unknown, all of the point estimates for ORR were [redacted] which suggests that the treatment benefit of dostarlimab was observed across all subgroups.

Figure 20: Forest plot of ORR (CR or PR) and 95% CI by subgroup by RECIST v1.1 in GARNET (efficacy population (N=[redacted]) (BICR)



Abbreviations: BOR: best overall response; BICR: blinded independent central review; CI: confidence interval; CPS: combined positive score; CR: complete response; dMMR: ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynaecology and Obstetrics; IHC: immunohistochemistry; PD: progressed disease; PD-L1: programmed cell death ligand; PR: partial response; sBLA: supplemental Biologics License Application; SD: stable disease.
Source: GSK Data on File.[13]

B.2.6 Meta-analysis

GARNET represents the only trial for dostarlimab. As such, no pooling of trials was undertaken, and this section is not applicable to this submission.

B.2.7 Indirect and mixed treatment comparisons

Two different approaches were employed in order to more closely match the comparative data in this submission (the UK RWE study and the published literature) and the data for dostarlimab in GARNET:

- **Dostarlimab versus current clinical management (UK RWE study MAIC versus GARNET):** The UK RWE study is included as the primary comparative efficacy evidence in this submission, given the large sample size of the study (N=[redacted]), together with the close alignment to patient characteristics in the GARNET trial and the real-world representation of current clinical management in this difficult to treat population. While the patient populations in GARNET and the GARNET-like cohort of the UK RWE study were closely aligned, a MAIC was conducted between GARNET and the UK RWE study for OS in order to investigate the impact of any remaining differences between the two populations. The methodology and results of this MAIC are presented in Section B.2.7.1.
- **Supportive comparative evidence for dostarlimab versus individual chemotherapy regimens:** Whilst the UK RWE study serves as the primary comparative efficacy evidence in this submission, a series of ITCs have also been conducted, where possible, between dostarlimab and the individual chemotherapy comparators listed in the NICE final scope, based on the published studies identified in the clinical SLR. These comparisons include a series of MAICs between GARNET and trials for carboplatin plus paclitaxel, paclitaxel monotherapy and doxorubicin monotherapy, as well as an inverse probability treatment weighting (IPTW) ITC between GARNET and the ZoptEC trial.[8-10] Given the limitations associated with the data identified in the literature, including the extremely limited data on patient characteristics and prognostic variables, and the resulting uncertainty associated with some of these analyses, they are provided for completeness as supportive comparative efficacy evidence only. The methodology and results of these analyses are presented in Section B.2.7.2.

A summary of the comparative efficacy evidence analyses considered in this submission is presented in Table 5 in Section B.2.2.

B.2.7.1 Dostarlimab versus current clinical management (UK RWE MAIC versus GARNET)

Overview

The methodology of the UK RWE study is detailed in Section B.2.3. The following section provides an overview of the MAIC between the patients in the ITT population of the GARNET trial and patients in the GARNET-like cohort of the UK RWE study. Additional details are presented in Appendix D.5.1.

Choice of MAICs

Due to the single-arm nature of the GARNET trial, and the UK RWE study, an unanchored MAIC was considered to represent the most appropriate and robust method for indirect comparison, in line with NICE TSD 18.[69]

The MAIC approach was preferred to simulated treatment comparisons (STCs) because MAICs produce marginal treatment effect estimates.[70] MAICs are conducted based on assigning differential weights to IPD available for the intervention (dostarlimab) which is similar to running logistic regression. An important part of any adjusted treatment comparison involves the identification of relevant prognostic variables and treatment effect modifiers. When these weights are applied, the aggregate measures on the modelled prognostic and treatment effect variables equal (or are as close as possible to) the values in the matched aggregate studies. This weighting approach produces a marginal (population level) treatment effect and therefore allows for a population-level indirect treatment comparison, which is an advantage over STCs, which produce only conditional (patient-level) treatment effects.

In addition, the key endpoint for this comparison (OS) is a survival endpoint. For survival endpoints, it is the number of OS events that occur, combined with the overall number of patients (rather than just the overall number of patients alone), that determines the effective sample size (and therefore, degrees of freedom), in any type of regression analysis. Since imbalances in covariates are accounted for using the weighting approach, covariates need not be adjusted for when modelling the outcome, meaning that the degrees of freedom is much closer to the number of patients once the analysis starts, maximising the number of prognostic and treatment effect modifying variables that can be considered, relative to using an STC approach.

MAIC methodology

The primary endpoint analysis considered in the UK RWE study MAIC utilised a Cox proportional hazards model, using weights obtained using the MAIC method, in order to estimate a HR for OS for patients receiving dostarlimab in GARNET versus patients receiving current clinical management in the GARNET-like cohort of the UK RWE study. A Cox proportional hazards model was considered feasible because the definition of OS was considered to be closely matched between GARNET and the UK RWE study.

However, it was not considered feasible to use a Cox proportional hazards model for PFS between GARNET and the UK RWE study, because PFS was not recorded in the UK RWE study (i.e. the NCRAS database does not include any data on progression, remission or recurrence of disease), and while TTNT was considered to be a suitable proxy, the measurement definitions and time-period evaluations associated with TTNT in the RWE population were considered to be too dissimilar to those for PFS in GARNET. Thus, TTNT in the RWE study was descriptively compared to PFS in the GARNET trial based on landmark PFS estimates at various timepoints, using the weighted GARNET IPD (following matching with the RWE population) versus the RWE GARNET-like cohort.

Identification of matching variables

A targeted literature review was conducted in May 2020 to identify a range of prognostic variables typically associated with survival in EC (detailed in Appendix M). The list of prognostic variables was subsequently validated with a panel of clinical experts from the UK, Germany and Canada. The clinical experts indicated that all of the prognostic variables identified would also

represent treatment effect modifying variables.

Based on the list of variables identified, the following variables were reported in the UK RWE study and considered for inclusion as matching variables (detailed in the following sections):

- Race/ethnicity (black, others, unknown versus white)
- Age category (≥65 years versus <65 years)
- ECOG PS status at treatment initiation (1 versus 0)
- Histology at initial diagnosis (non-endometrioid, unknown versus endometrioid)
- FIGO stage at initial diagnosis (Stage III/IV versus Stage I/II)
- Grade of disease at diagnosis (Grade 3/4, unknown versus Grade 1/2)
- Number of prior platinum-based therapies (0 or 1 versus ≥2)
- Prior surgery for study indication (yes versus no)

Based on this list, the modification and prognostic value of each potential matching variable was investigated using a Cox proportional hazard model. In this model, the outcome variable (OS or PFS) was modelled as a function of each variable of interest. Cox regression models were fit separately for the GARNET data and the RWE data. Patient characteristics that exhibited association at level of significance p≤0.1 in at least one of the two datasets were considered prognostic.

Based on these results, two scenarios were constructed, based on the prognostic variables identified by clinical expert opinion (Scenario 1) and the matching variables found to be statistically significant based on regression analyses (Scenario 2).

Grade was not found to be statistically significant by the regression analysis, but was identified as a prognostic variable by clinical experts. Unfortunately, grade was challenging to include in the adjustment because a large number of patients in the UK RWE GARNET-like cohort ([redacted]%) had an 'unknown grade', compared to [redacted]% in the GARNET cohort.

Clinical experts confirmed that grade information was unlikely to be missing from the UK RWE study at random, and therefore, the potential for an underlying difference in this [redacted]% of patients relative to the remaining proportion of patients in the UK RWE GARNET-like cohort means that the use of grade as a matching variable is associated with substantial uncertainty. If grade is included in the analysis, it results in a requirement to heavily up-weight the few patients in the GARNET cohort with an unknown grade (as shown in Figure 21), which drastically reduces the ESS to N=[redacted] (i.e., a [redacted]% reduction in the ESS compared to the original sample of N=129), leading to unreliable results.

Figure 21: Histogram of the weights assigned to patients in the GARNET ITT population in the MAIC versus the UK RWE GARNET-like population using the matching variables in Scenario 1 in addition to grade

Abbreviations: ITT: intention-to-treat; MAIC: matching adjusted indirect comparison; RWE: real-world evidence; UK: United Kingdom.

As a result, grade was excluded from the list of matching variables considered in Scenario 1, which included histology (non-endometrioid and unknown versus endometrioid) and the number of lines of prior platinum-based therapy in the advanced/recurrent setting (0 or 1 versus ≥2) as matching variables, based on clinical expert opinion. Scenario 1 was considered robust, with a relatively large sample size of N=[redacted] (a reduction of [redacted]% compared to the original sample of N=129), more than twice the effective sample size compared to also including grade as a matching variable.

Scenario 2 considered the matching variables identified as statistically significant by regression analysis (further details of the regression analysis are presented Appendix D.5.1). For the UK RWE GARNET-like cohort, these variables consisted of: race/ethnicity (black, others, unknown versus white), stage at diagnosis (Stage III/IV versus Stage I/II), histology (non-endometrioid, unknown versus endometrioid) and prior surgery (yes versus no). The ESS in Scenario 2 was highly comparable to Scenario 1; Scenario 2 resulted in an ESS of N=[redacted] (a [redacted]% reduction compared to the original sample of N=129).

The two scenarios and the matching variables considered in each, based on clinical expert opinion (Scenario 1) and the regression analysis (Scenario 2), are detailed in Table 84. Further details on prognostic matching, including the regression analyses, characteristics of the matched populations for each scenario, histograms of the weighting of the GARNET cohorts for each scenario, the process for determination of treatment effect modifiers and assessments of proportional hazard can be found in Appendix D.5.1.

Table 23: Scenarios considered in the UK RWE study MAICs versus GARNET

Scenarios	Prognostic variables
Scenario 1	• Histology[a] • Number of prior platinum-based therapies in the advanced/recurrent setting[b]
Scenario 2	• Race/ethnicity • Stage at diagnosis • Histology[a] • Prior surgery

Footnotes: [a] For scenarios including histology as a matching variable, one patient with an "unknown" histology was removed from the GARNET cohort in order to achieve balance. [b] For scenarios including the number of prior platinum-based therapies, patients with 0 or ≥2 prior platinum-based therapies from the GARNET cohort were removed in order to achieve balance.
Abbreviations: MAIC: matching-adjusted indirect comparison; RWE: real-world evidence.

Results

Overall survival

The results of both matching scenarios showed that the median OS, as well as the percentage of patients alive at Month 6, 12 and 18, was greater for patients treated with dostarlimab versus patients treated with current clinical management. The HRs for OS (dostarlimab versus current clinical management) showed that dostarlimab statistically significantly reduced the risk of death versus current clinical management in both scenarios.

Scenario 1 and Scenario 2 both found that a slightly improved OS, compared to the unadjusted GARNET ITT population. At Month 12, [redacted]% of patients were alive in the unadjusted ITT population, compared to [redacted]% of patients in scenario 1, and [redacted]% of patients in scenario 2. The results of the unadjusted population and scenario 1 were similar at Month 18, with [redacted]% and [redacted]% of patients still alive, while scenario 2 found that [redacted]% of patients were still alive at Month 18. The OS HR between dostarlimab and current clinical management is [redacted] (95% CI: [redacted], [redacted]) when including the unadjusted GARNET ITT population, compared to [redacted] (95% CI: [redacted], [redacted]) in Scenario 1 and [redacted] (95% CI: [redacted], [redacted]) in Scenario 2.

The similarity of the OS results between the unadjusted GARNET ITT population and both matched scenarios indicate that there were minimal differences between the GARNET ITT population and the UK RWE GARNET-like population, and suggests that any differences between the two populations could mean that the OS benefit of dostarlimab is slightly underestimated in the unadjusted comparisons presented previously in this submission.

OS for the UK RWE GARNET-like cohort and the GARNET ITT population before and after matching (Scenario 1 and 2) is presented in Table 24. KM curves for PFS prior to adjustment of the GARNET population are presented in Figure 22, and KM curves for PFS including the adjusted GARNET populations are presented in Figure 23 (Scenario 1), and Figure 24 (Scenario 2), respectively.

Table 24: OS for patients in the GARNET ITT population (before and after matching) and the UK RWE GARNET-like cohort

	UK RWE GARNET-like cohort (N=[redacted])	GARNET ITT population prior to matching (N=129)	Adjusted GARNET population (Scenario 1)	Adjusted GARNET population (Scenario 2)
ESS	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS rate at 6 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS rate at 12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

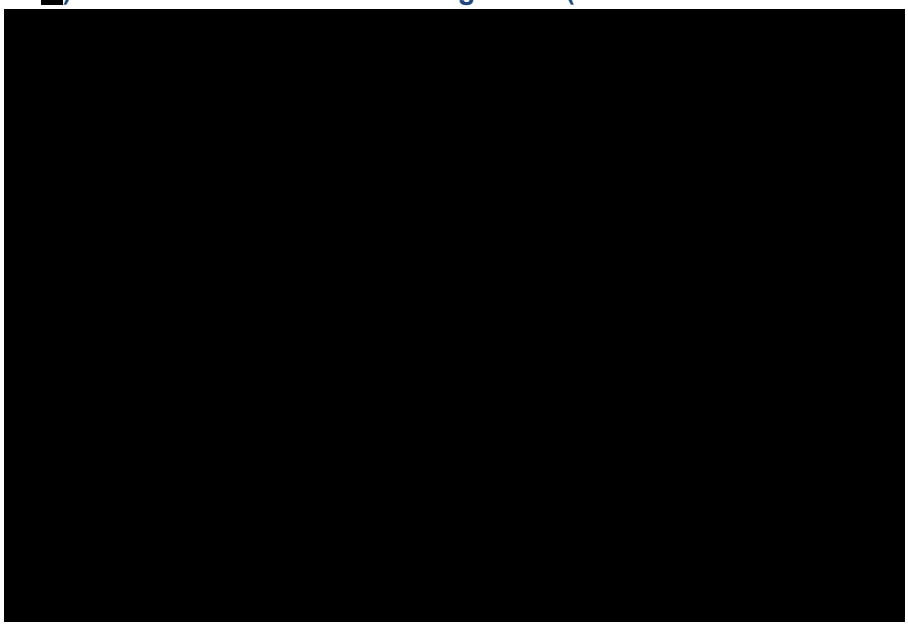
OS rate at 18 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio for OS (95% CI) for dostarlimab versus current clinical management	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; ESS: effective sample size; ITT: intention-to-treat; NA: not applicable; NR: not reached; OS: overall survival; RWE: real-world evidence.

Figure 22: OS KM curves – dostarlimab (unadjusted GARNET ITT population, N=129) versus current clinical management (UK RWE GARNET-like cohort, N=[redacted])

Abbreviations: ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival; RWE: real-world evidence.

Figure 23: OS KM curves – dostarlimab (adjusted GARNET population, Scenario 1, ESS N=[redacted]) versus current clinical management (UK RWE GARNET-like cohort, N=[redacted])



Abbreviations: ESS: effective sample size; ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival; RWE: real world evidence.

Figure 24: OS KM curves – dostarlimab (adjusted GARNET population, Scenario 2, ESS N=[redacted]) versus current clinical management (UK RWE GARNET-like cohort, N=[redacted])

Abbreviations: ESS: effective sample size; ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival; RWE: real world evidence.

Progression-free survival

Comparison of PFS for the adjusted GARNET cohorts in Scenario 1 and Scenario 2 suggested that, once the GARNET ITT population and the GARNET-like RWE population are more closely matched, dostarlimab provides a slightly greater PFS benefit versus current clinical management, when compared with the unadjusted comparison between the two. However, the generally similar PFS results indicate that the two populations were closely matched prior to adjustment, providing confidence in the unadjusted comparisons described in Section B.2.4.5.2.

The median PFS for patients receiving dostarlimab increases in Scenario 1 and Scenario 2, to [redacted] months (95% CI: [redacted], [redacted]) and [redacted] months (95% CI: [redacted], [redacted]), respectively, compared to the median PFS of [redacted] months (95% CI: [redacted], [redacted]) in the GARNET ITT population.

The landmark estimates show that the percentage of patients treated with dostarlimab who are progression-free are largely similar before and after adjustment. At Month 12, [redacted]% of patients treated with dostarlimab were progression-free in the unadjusted population, compared to [redacted]% in Scenario 1 and [redacted]% in Scenario 2. By Month 18, [redacted]% of patients were progression-free in the unadjusted population, compared to [redacted]% in Scenario 1 and [redacted]% in Scenario 2.

PFS for the UK RWE GARNET-like cohort and the GARNET ITT population before and after matching (Scenario 1 and 2) is presented in Table 25. KM curves for PFS prior to adjustment of the GARNET population are presented in Figure 25, and KM curves for PFS including the adjusted GARNET populations are presented in Figure 26 (Scenario 1), and Figure 27 (Scenario 2), respectively.

The median PFS of [redacted] (95% CI: [redacted], [redacted]) months for the unadjusted GARNET ITT population in Table 25 is different to the median PFS for the GARNET ITT population of [redacted] (95% CI: [redacted], [redacted]) months presented in Section B.2.4.5, due to rounding of individual patient PFS times to one decimal place for the MAIC versus the UK RWE study, but were not rounded in the PFS analysis of the GARNET ITT cohort presented in Section B.2.4.5.

Due to the plateauing of the PFS curve for patients treated with dostarlimab when approximately [redacted] of patients are progression-free, [redacted], [redacted] (as previously detailed in Section B.2.4.7) [redacted]. Rounding of individual patient PFS estimates results in the KM curve staying above [redacted]% until [redacted] months, versus [redacted] months when the individual patient PFS estimates are not rounded.

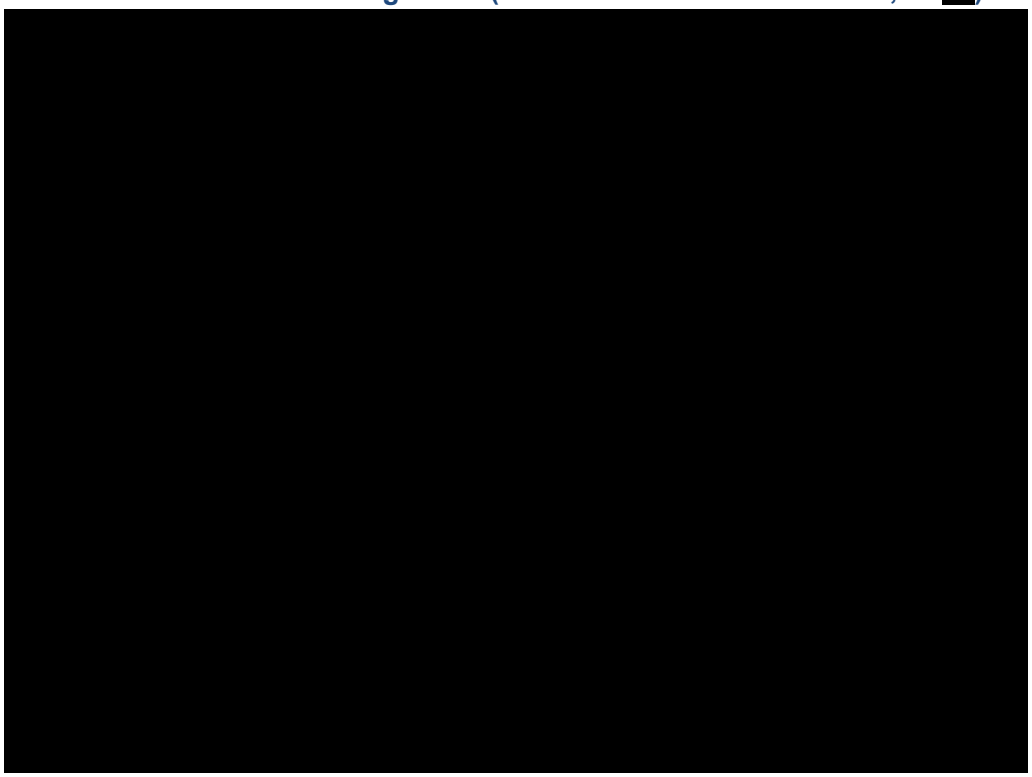
Table 25: PFS for patients in the GARNET ITT population (before and after matching) and the UK RWE GARNET-like cohort

	UK RWE GARNET-like cohort (N=[redacted])[a]	GARNET ITT population prior to matching (N=129)	Adjusted GARNET population (Scenario 1)	Adjusted GARNET population (Scenario 2)
ESS	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PFS rate at 6 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PFS rate at 12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

PFS rate at 18 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

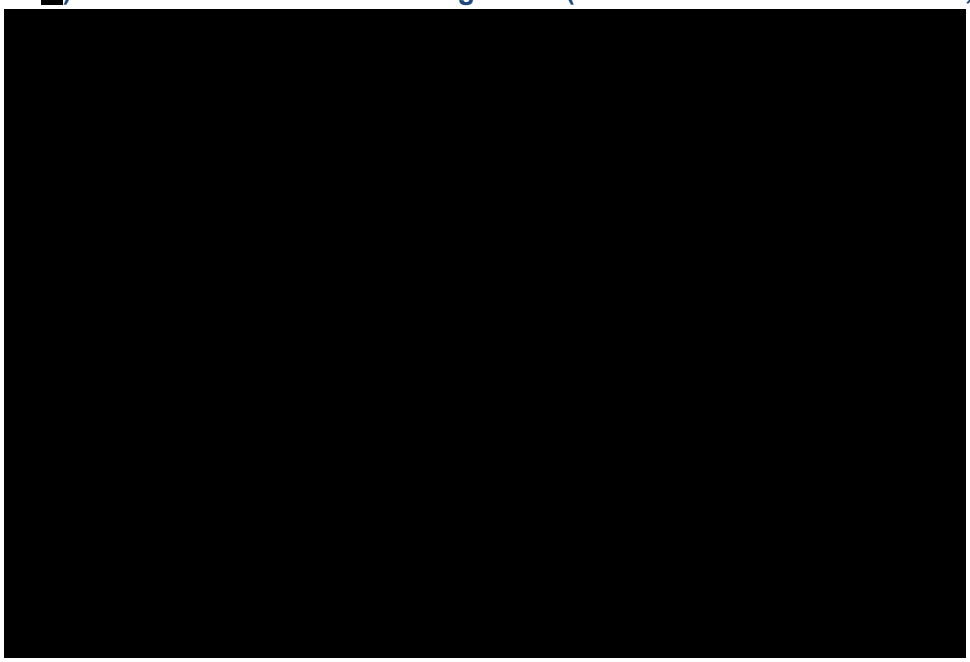
Footnotes: [a] The results presented for the UK RWE GARNET-like cohort use TTNT as a proxy for PFS, as PFS was not recorded in the NCRAS database. [b] The median PFS for GARNET presented here is different to the median PFS preented for the GARNET ITT population in Section B.2.4.5 due to rounding of individual patient PFS estimates in the analysis presented above, which means the KM curve stays above 50% until [redacted] months.
Abbreviations: CI: confidence interval; ESS: effective sample size; ITT: intention-to-treat; NCRAS: National Cancer Registry Analysis System; NR: not reached; PFS: progression free survival; RWE: real-world evidence; TTNT: time to next treatment.
Source: GSK Data on File.[13]

Figure 25: PFS KM curves – dostarlimab (unadjusted GARNET ITT population, N=[redacted]) versus current clinical management (UK RWE GARNET-like cohort, N=[redacted])



Abbreviations: ITT: intention-to-treat; KM: Kaplan-Meier; PFS: progression-free survival; RWE: real-world evidence.
Source: GSK Data on File.[13]

Figure 26: PFS KM curves – dostarlimab (adjusted GARNET population, Scenario 1, ESS N=[redacted]) versus current clinical management (UK RWE GARNET-like cohort, N=[redacted])



Abbreviations: ESS: effective sample size; ITT: intention-to-treat; KM: Kaplan-Meier; PFS: progression-free survival; RWE: real world evidence.
Source: GSK Data on File.[13]

Figure 27: PFS KM curves – dostarlimab (adjusted GARNET population, Scenario 2, ESS N=[redacted]) versus current clinical management (UK RWE GARNET-like cohort, N=[redacted])

Abbreviations: ESS: effective sample size; ITT: intention-to-treat; KM: Kaplan-Meier; PFS: progression-free survival; RWE: real-world evidence.
Source: GSK Data on File.[13]

Additional results

Additional results, including the patient characteristics of the unadjusted and adjusted populations, the histograms of weightings for each adjusted population, and the assessment of

proportional hazards, are presented in Appendix D.5.1. Furthermore, the results of the MAIC between GARNET and the UK RWE GARNET-like ECOG PS ≤1 population are presented as a sensitivity analysis in Appendix D.5.1.

Conclusions

The results of the UK RWE ITC present clear supportive evidence that patients treated with dostarlimab experience a significant and substantially decreased risk of disease progression or death compared to patients receiving current clinical management for the treatment of recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen in the UK.

The similarity of the PFS and OS results for the unadjusted GARNET ITT cohort and the adjusted GARNET cohorts in Scenario 1 (matching based on the most important prognostic variables according to UK clinical expert feedback, excluding grade) and Scenario 2 (matching based on prognostic variables as identified by regression analyses) suggests that the two populations are closely matched, with minimal differences with respect to key prognostic variables. Moreover, the results show that the remaining differences between the GARNET ITT population and the UK RWE GARNET-like cohort may actually result in an underestimation of the true PFS and OS benefit that dostarlimab provides versus current clinical management; the unadjusted OS HR between dostarlimab and current clinical management was [redacted] (95% CI: [redacted], [redacted]), compared to adjusted OS HRs of [redacted] (95% CI: [redacted], [redacted]) in Scenario 1 and [redacted] (95% CI: [redacted], [redacted]) in Scenario 2, respectively.

Based on the strengths of the UK RWE study, and the results of the above comparison, the unadjusted UK RWE GARNET-like cohort is used in the base case-cost effectiveness analysis, while scenarios are considered based on the adjusted scenarios presented in this section (as described in B.3.8.3).

B.2.7.2 Supportive comparative evidence for dostarlimab versus individual chemotherapy regimens

B.2.7.2.1 ITC between dostarlimab (GARNET) and doxorubicin (ZoptEC study)

Overview

As detailed above and in Appendix D, during the data extraction phase of the clinical SLR, it became apparent that there was a paucity of data for the comparator chemotherapy studies, which would impact the robustness of any ITCs. As such, GSK contacted the corresponding authors of each of the relevant chemotherapy studies identified from the SLR in order to request further data.

Following this, Aeterna Zentaris, the sponsoring company of the ZoptEC study provided IPD for the ZoptEC study.[8-10] Using this IPD, an adjusted comparison of OS between dostarlimab and doxorubicin monotherapy was conducted. The OS comparison was performed using a Cox proportional hazards model with stabilised inverse probability of treatment weighting (IPTW) to estimate an HR for OS between dostarlimab and doxorubicin. The IPTW approach minimises the standardised differences between the baseline characteristics of two populations, and allows for two separate populations to be compared with as little bias as possible. This approach is aligned with NICE TSD 17.[71]

It was not possible to use IPTW to estimate a HR for PFS between dostarlimab and doxorubicin, due to differences in the definition of PFS and the timepoints of tumour assessments between GARNET and ZoptEC.[8-10] PFS was defined from the date of the first dose of dostarlimab in GARNET, but defined as the time elapsed from randomisation in ZoptEC.[8-10] Patients were assessed every six weeks for disease progression starting from Week 12 in GARNET; conversely, patients were re-evaluated for response every nine weeks in ZoptEC.[8-10] A summary of the PFS definitions in both studies is presented in Appendix D.5.2. Due to the differences in PFS between the two studies, a descriptive-only KM analysis was conducted to compare PFS between GARNET and ZoptEC.[8-10]

Whilst the results of this ITC provide a comparison versus only one of the relevant chemotherapy comparators (doxorubicin monotherapy), and the UK RWE study detailed in Section B.2.7.1 represents the primary comparative efficacy evidence in this submission, this ITC was nevertheless still conducted to provide an alternative analysis for consideration within a scenario analysis in the economic analysis (see Section B.3.8.3).

A summary of the methodology is provided below; the full methodology can be found in Appendix D.5.2.

Application of exclusion criteria to GARNET and ZoptEC

Prior to the statistical analysis, it was necessary to consider the inclusion/exclusion criteria and baseline characteristics of the GARNET and ZoptEC studies, and to apply a series of additional exclusion criteria to each trial in order to match the two populations as closely as possible.

Patients were excluded from the ZoptEC trial if they had a follow-up greater than 36 months, or if they did not have an ECOG PS score of 0 or 1.[8-10] Patients were excluded from the GARNET trial if they had previously received more than one prior platinum-based therapy.

The exclusion of these patients reduced the patient populations to N=[redacted] patients in GARNET and N=[redacted] patients in ZoptEC.[8-10] These populations are known as **the main analysis sets** used throughout this ITC. A summary of the exclusion criteria applied and the patients excluded at each step is detailed in Appendix D.5.2.

IPTW ITC methodology

As detailed in Section B.2.7.1, a targeted literature review was conducted in May 2020 to identify a range of prognostic variables typically associated with survival in EC (detailed in Appendix M). The list of prognostic variables was subsequently validated with a panel of clinical experts from the UK, Germany and Canada. The clinical experts indicated that all of the prognostic variables identified would also represent treatment effect modifying variables.

Of the prognostic variables identified, the following variables were reported in the ZoptEC study and used for estimating stabilised-IPTW in this analysis:[8-10]

- Age (<65 years versus >65 years)
- Race (non-white versus white)
- ECOG PS score (0 or 1 versus 2)
- Histology (endometrioid versus non-endometrioid)
- Most recent FIGO stage at Baseline (Stage I/II versus Stage III/IV)

- Prior surgery (no versus yes)

While grade of disease was also reported in ZoptEC, grade could not be used for estimating stabilised IPTW because it causes a violation of the positivity assumption, as detailed in Appendix D.5.2.

IPTW ITC results

Overall survival

The results of the IPTW ITC versus doxorubicin monotherapy based on the ZoptEC study are presented in B.2.7.2, and the adjusted KM curves are presented in Figure 28 and summarised in Table 27.[8-10] The comparison showed that treatment with dostarlimab resulted in a significant and marked reduction in the risk of death versus doxorubicin monotherapy. Patients treated with dostarlimab were [redacted]% less likely to die at any given timepoint compared to patients receiving doxorubicin monotherapy (HR: [redacted]; 95% CI: ([redacted], [redacted]); p[redacted]).

Table 26: Results for the safety analysis data set on OS with adjusting stabilised-IPTW

	N	HR between dostarlimab and doxorubicin (95% CI)	Standard error	p-value
Cox PH model	[redacted]	[redacted]	[redacted]	[redacted]
Assumption check	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; IPTW: inverse probability treatment weighting; OS: overall survival; PH: proportional hazards.
Source: GSK Data on File.[13]

Figure 28: OS KM curves – dostarlimab (adjusted GARNET main analysis set, N=[redacted]) versus doxorubicin monotherapy (adjusted ZoptEC main analysis set, N=[redacted] following adjustments based on IPTW[8-10]

Footnotes: The number at risk with IPTW adjustment may differ slightly from the total sample size. This is because the number at risk has been weighted by IPTW. The IPTW weighted number at risk may not be an

integer and in the KM plots the weighted IPTW number at risk has been rounded to the nearest integer value.
Abbreviations: KM: Kaplan-Meier; OS: overall survival; TRT: treatment.
Source: GSK Data on File.[13]

Table 27: Summary of OS with adjusting stabilised-IPTW for the main analysis data set

	Dostarlimab (N=[redacted])	Doxorubicin (N=[redacted])
OS status, n (%)		
Event	[redacted]	[redacted]
Censored	[redacted]	[redacted]
OS by quartile (95% CI), months		
25th percentile	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75th percentile	[redacted]	[redacted]
Log-rank test p-value	[redacted]	

Abbreviations: CI: confidence interval; IPTW: inverse probability treatment weighting; NR: not reached; OS: overall survival.
Source: GSK Data on File.[13]

Additional results including the patient characteristics for both populations before and after matching, checking of effect modifiers and assessments of proportional hazards and unmeasured confounding, are presented in Appendix D.5.2.

Overall survival (sensitivity analysis)

In the primary IPTW analysis, [redacted] patients were removed from the analysis across GARNET and ZoptEC to ensure comparability between the two populations.[8-10] A sensitivity analysis was conducted where [redacted] of these [redacted] patients, who were excluded in the main analysis (detailed in Appendix D.5.2) are included, resulting in a total sample size of N=[redacted], with N=129 patients in GARNET and N=[redacted] patients in ZoptEC (it was still necessary to exclude [redacted] patient in ZoptEC because they did not have a baseline ECOG PS, so could not be included).[8-10]

The results of the sensitivity analysis showed that patients treated with dostarlimab were [redacted]% less likely to die at any given timepoint compared to patients receiving doxorubicin monotherapy (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]). The similarity between the two point estimates in the main analysis (HR: [redacted]; 95% CI: ([redacted], [redacted]); p[redacted]). and the sensitivity analysis (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]). The provides confidence that treatment with dostarlimab results in approximately a [redacted]% reduced risk of death compared to doxorubicin monotherapy.

Full details for this sensitivity analysis are presented in Appendix D.5.2.

Progression-free survival

As outlined previously, it was not possible to conduct an IPTW ITC for PFS, due to differences in the definitions of PFS and the timepoints of tumour assessments between GARNET and ZoptEC, as detailed in Section B.2.7.2.1 and Appendix D.5.2.[8-10] PFS was defined from the date of the first dose of dostarlimab in GARNET, but defined as the time elapsed from randomisation in ZoptEC.[8-10] Patients were assessed every six weeks for disease progression starting from Week 12 in GARNET; conversely, patients were re-evaluated for response every nine weeks in ZoptEC.[8-10] A summary of the PFS definitions in both studies is presented in Appendix D.5.2.

However, a supportive comparative analysis was conducted, investigating PFS for dostarlimab versus doxorubicin once the additional exclusion criteria outlined previously had been applied to match the populations of GARNET and ZoptEC more closely. The KM curves for PFS for dostarlimab (GARNET main analysis set, N=[redacted]) and doxorubicin (ZoptEC main analysis set, N=[redacted]) are presented in B.2.7.2 below, and a summary of the PFS from the two studies is presented in B.2.7.2.

The results showed that dostarlimab provided a significant PFS benefit for patients compared to doxorubicin monotherapy after initial adjustment between the two studies. A clear plateau in the dostarlimab PFS curve can be observed in Figure 29 when approximately [redacted]% of patients were progression-free. Conversely, there was no such plateau was observed for patients treated with doxorubicin monotherapy; almost all of the patients treated with doxorubicin had experienced disease progression or death prior to Month 24.

Figure 29: PFS KM curves – dostarlimab (GARNET main analysis set, N=[redacted]) versus doxorubicin (ZoptEC main analysis set, N=[redacted])[8-10]

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; TRT: treatment.
Source: GSK Data on File.[13]

Table 28: Summary of PFS for the main analysis data set

	Dostarlimab (N=[redacted])	Doxorubicin (N=[redacted])
PFS status, n (%)		
Event	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Quartile (95% CI)		
25th percentile	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75th percentile	[redacted]	[redacted]

Footnote: This analysis does not consider the differences in tumour assessment schedules between GARNET and ZoptEC detailed in Section B.2.7.2.1 and Appendix D.5.2.

Abbreviations: CI: confidence interval; IPTW: inverse probability treatment weighting; NR: not reached; PFS: progression-free survival.
Source: GSK Data on File.[13]

B.2.7.2.2 MAICs versus carboplatin plus paclitaxel, paclitaxel monotherapy and doxorubicin monotherapy

Overview

As IPD were available for the ZoptEC study identified in the clinical SLR, a separate ITC was conducted between GARNET and ZoptEC, as described above.[8-10] The remaining relevant studies identified in the clinical SLR were reviewed for inclusion in a series of MAICs between dostarlimab and the individual chemotherapy comparators listed in the NICE final scope. Given the significant limitations associated with the MAICs presented below, the results of these MAICs provide supportive comparative efficacy evidence for this submission only.

Feasibility assessment

Of the 13 studies included in the clinical SLR, only studies including the individual chemotherapy regimens listed in the NICE final scope were considered for inclusion within the MAIC feasibility assessment:

- Re-challenge with carboplatin plus paclitaxel
- Paclitaxel monotherapy
- Doxorubicin monotherapy
- Carboplatin monotherapy

An overview of the trials identified in the clinical SLR and the details of the trials that were included and excluded from the MAICs is presented in Appendix D.5.3.

As part of the feasibility assessment, eight studies included in the clinical SLR were excluded from the series of MAICs. Three studies were excluded because the study regimen was not listed as a relevant comparator in the NICE final scope, and two studies were excluded because they did not report KM curves for OS. Other reasons for exclusion were that the study considered a population that was considered too different to GARNET with respect to race for a comparison to be feasible (N=1), and that the study reported data by platinum-free interval which was not reported as a covariate in other studies (N=1). Finally, GSK were able to obtain IPD for the ZoptEC study, and so the ZoptEC study was excluded from the series of MAICs, but a separate ITC versus ZoptEC was considered as described above in Section B.B.2.7.2.1, in line with NICE TSD 17 and 18.[8-10, 69, 71]

MAIC methodology

A summary of the MAIC methodology is provided below. The detailed methodology underlying the MAICs, including the programming code used, is presented in Appendix D.5.3.

Choice of MAICs

MAICs were chosen as the most appropriate and robust method for the indirect comparisons with the studies identified in the published literature, in line with NICE TSD 18[69] and the reasons outlined in Section B.2.7.1, considering the single-arm nature of the GARNET trial and four of the five trials included in the series of MAICs, and the consideration of survival outcomes (PFS and

OS).

Matching of the study populations

The first step in the conduct of the MAICs involved the removal of patients from the base GARNET dataset that would not have met the matched study inclusion/exclusion criteria and baseline characteristics range criteria in each of the comparator studies (where data identification was feasible). A summary of the patients removed from the base GARNET population for each of the MAICs is presented in Appendix D.5.3.

Further to this, the unanchored MAIC methodology was applied to the reduced set of GARNET patients, in line with the approach described in NICE TSD 18.[69] The process considers two inputs: the mean values of the prognostic/treatment effect modifying variables in the non-GARNET study, and the individual matching data from GARNET. The methodology then utilises a method of moments analytical technique (as listed in NICE TSD 18[69]) to produce individual patient specific weights (for GARNET patients), that when applied, produce weighted prognostic means that approximately equal those inputted from the aggregate study.

As previously detailed, a targeted literature review was conducted in May 2020 to identify a range of prognostic variables typically associated with survival in EC (detailed in Appendix M). The list of prognostic variables was subsequently validated with a panel of clinical experts from the UK, Germany and Canada. The clinical experts indicated that all of the prognostic variables identified would also represent treatment effect modifying variables.

Based on the list of variables identified, the following variables were reported in the published studies included in the series of MAICs, and were included as matching variables:

- Age
- Race
- Number of prior anti-cancer treatments
- Histology (endometrioid type I only versus others)
- Prior surgery for the study indication (yes versus no)
- ECOG PS score (before comparator treatment start date)
- Most recent FIGO stage (before comparator treatment start date)

Grade was also identified as an important prognostic variable by clinical experts, however none of the studies identified in the clinical SLR reported sufficient data on grade (the only study to report any information on grade was Makker *et al.* (2013), which reported extremely limited data). The MAIC weights were then applied to the GARNET PFS/OS data using an appropriate modelling process to produce contrast estimates against the comparator in the comparator study. The KM curves of the comparator studies were digitised (using Engauge Digitizer 10.2 software[72]), and the algorithm detailed in Guyot *et al.* (2012) was utilised to produce pseudo-individual patient data for PFS/OS from the aggregate trial data.[73] A weighted Cox regression was then applied to this dataset, combining the pseudo-IPD with the GARNET data (no covariates other than treatment). A weight of one was assigned to each patient from the pseudo-IPD of the comparator study; the MAIC-calculated weight was assigned to each patient in GARNET.

Full details on the MAIC methodology, including details of the assessment of proportional hazards and quantitative bias analyses, are provided in Appendix D.5.3.

MAIC results

A summary of the MAIC results are presented in this section; additional results, as well as quantitative bias analyses and proportional hazard assessments associated with each of the MAICs are presented in Appendix D.5.3.

Study characteristics

A total of five studies were included in the series of MAICs in addition to GARNET (B.2.7.2). McMeekin *et al.* (2015)[6] was a Phase III, open-label trial which compared one group of patients that received either paclitaxel monotherapy or doxorubicin monotherapy to a group of patients receiving ixabepilone.[6] Of the remaining four trials, three were retrospective studies investigating carboplatin plus paclitaxel (Rubinstein *et al.* [2019]) and doxorubicin monotherapy (Julius *et al.* [2013] and Makker *et al.* [2013]).[7, 11, 59] The final study, Mazgani *et al.* (2008), was a cohort study investigating carboplatin plus paclitaxel.[60]

Patient characteristics were poorly reported across the comparator studies. Of the most important prognostic variables identified above, none of the comparator studies reported information on the number of prior anti-cancer treatments, prior surgery for the study indication, grade or MMR/MSI molecular profile type. In particular, the paucity of data on prior anti-cancer treatments is a key limitation, as this was included alongside histology, grade and ECOG PS status as the most important prognostic variables based on clinical expert opinion.

Prognostic variables were particularly limited in the Julius *et al.* (2019), Rubinstein *et al.* (2019) and Mazgani *et al.* (2008) studies.[7, 59, 60] None of these studies reported any information on ECOG PS, while only Makker et al. (2013) reported extremely limited data on grade. Data on histology, race and age were also poorly reported (detailed in B.2.7.2). Given the extremely limited data available, as well as small sample sizes, the MAICs versus these studies must be interpreted with particular caution, given the substantial uncertainty and unknown potential for bias.

Of the two studies reporting more comprehensive details on prognostic variables, it is clear that patients in McMeekin *et al.* (2015)[6] are most closely aligned with those is GARNET. Notably, both GARNET and McMeekin *et al.* (2015) excluded patients with an ECOG PS ≥ 1, although GARNET included slightly more patients with PS 1 versus McMeekin *et al.* (2015)[6] ([redacted]% versus 33% of patients with an ECOG PS of 1).

However, the inclusion of 12% of patients with an ECOG PS of 2 represents a key limitation of the MAICs versus Makker *et al.* (2013).[11] There were [redacted] patients with an ECOG PS of 2 in GARNET, and therefore the IPD of GARNET cannot be adjusted to account for this imbalance between the two studies, likely resulting in a slight bias in favour of dostarlimab.

A summary of the patient characteristics reported in each study, as well as additional details about each of the studies is presented in Appendix D.5.3.

Progression-free survival

PFS data were only available from three of the five studies that were included from the MAIC feasibility assessment, allowing MAICs to be conducted versus doxorubicin monotherapy and

carboplatin plus paclitaxel only.

An overview of the MAIC results for PFS is provided in Table 29. PFS KM curves for dostarlimab (pre- and post-MAIC weighting) versus each of the comparators are provided in Figure 30 (dostarlimab versus doxorubicin monotherapy) as well as Figure 31 and Figure 32 (dostarlimab versus carboplatin plus paclitaxel), respectively.

Compared with doxorubicin monotherapy, results from the MAIC versus Makker *et al.* (2013) demonstrate that dostarlimab significantly reduces the risk of disease progression versus doxorubicin monotherapy.[11] Of note, patients treated with dostarlimab were more than five times less likely to experience disease progression or death (HR: [redacted]; 95% CI: [redacted], [redacted]; p[redacted]) versus patients treated with doxorubicin monotherapy based on evidence derived from Makker *et al.* (2013).[11] Even when considering the upper-most CIs, patients treated with dostarlimab still experienced more than a three times reduced risk of disease progression or death (HR: [redacted]). These results clearly indicate that dostarlimab provides a PFS benefit versus doxorubicin monotherapy, even if the magnitude of the PFS benefit is uncertain, given the inherent limitations with Makker *et al.* (2013).[11]

The results of the PFS MAICs versus Rubinstein *et al.* (2019) and Mazgani *et al.* (2008) are more uncertain, and indicate that no significant differences in PFS between patients treated with dostarlimab and patients treated with carboplatin plus paclitaxel.[59, 60]

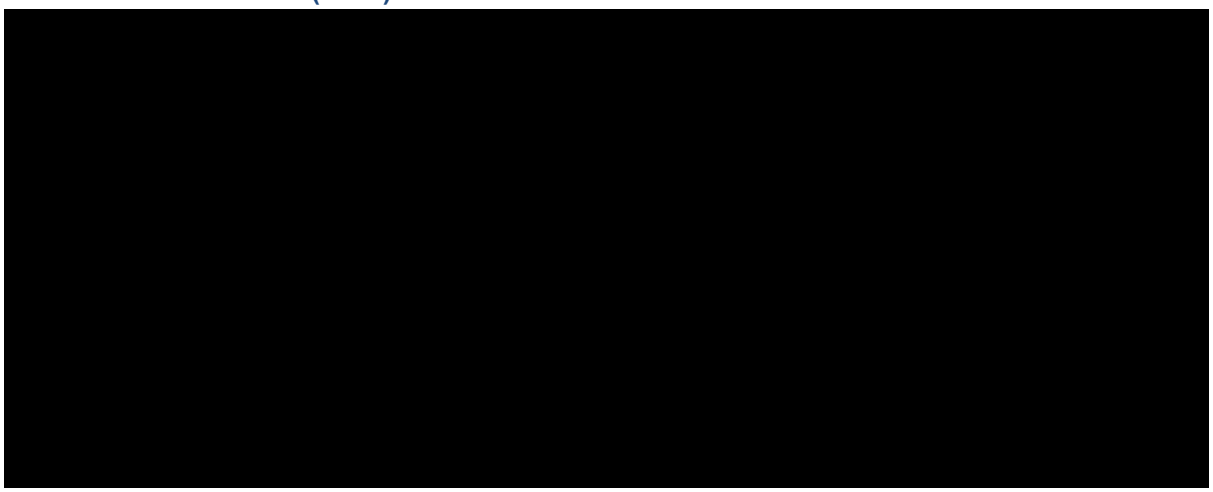
However, in addition to the wide CIs which introduce uncertainty, there are a number of limitations associated with these MAICs, including the limited sample sizes, paucity of patient characteristic data, while Mazgani et al. (2008) based tumour assessment on RECIST v1, compared to GARNET which used RECIST v1.1.[60] As such, it is difficult to draw any meaningful conclusions about the PFS benefit of dostarlimab relative to carboplatin plus paclitaxel based on the results of these MAICs.

Table 29: PFS hazard ratios derived from the MAICs

Comparator	Reference (author, year)	MAIC	
		HR (95% CI)	p-value
Paclitaxel or doxorubicin[a]	McMeekin *et al.* (2015)[6]	NA[b]	NA
Doxorubicin	Makker *et al.* (2013)[11]	[redacted]	[redacted]
PLD	Julius *et al.* (2013)[7]	NA[b]	NA
Carboplatin plus paclitaxel	Rubinstein *et al.* (2019)[59]	[redacted]	[redacted]
Carboplatin plus paclitaxel	Mazgani *et al.* (2008)[60]	[redacted]	[redacted]

Footnotes: [a] Patients in the McMeekin *et al.* (2015)[6] study received either paclitaxel or doxorubicin. Clinical expert opinion indicated that the efficacy between the two treatments is likely to be similar, and therefore it is appropriate to consider this as one combined arm. [b] McMeekin et al. (2015) and Julius et al. (2013) did not report PFS KM curves, and therefore MAICs could not be conducted for PFS.[6, 7]
Abbreviations: CI: confidence interval; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; NA: not applicable; PLD: pegylated liposomal doxorubicin.
Source: GSK Data on File.[13]

Figure 30: MAIC PFS KM curves for dostarlimab based on GARNET versus doxorubicin based on Makker *et al.* (2013)[11]



Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival.
Source: GSK Data on File.[13]

Figure 31: MAIC PFS KM curves for dostarlimab based on GARNET versus carboplatin plus paclitaxel based on Rubinstein *et al.* (2019)[59]

Footnotes: It is likely that the MAIC between dostarlimab and carboplatin plus paclitaxel based on Rubinstein *et al.* (2019) violates the proportional hazards assumption (further detailed in Appendix D.5.3), although it is difficult to say this definitively due to the small number of patients include in Rubinstein *et al.* (2019).[59] Nonetheless, there are no viable alternatives to the proportional hazards assumption, as Rubinstein *et al.* (2019) does not report sufficient data to be able to estimate time varying hazard ratios.[59]
Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival.
Source: GSK Data on File.[13]

Figure 32: MAIC PFS KM curves for dostarlimab based on GARNET versus carboplatin plus paclitaxel based on Mazgani *et al.* (2008)[60]

Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival.
Source: GSK Data on File.[13]

Overall survival

The primary results of the MAICs between dostarlimab and individual studies of the relevant chemotherapy comparators listed in the NICE final scope are presented in Table 30.

The KM plots of OS for the pre-MAIC unweighted and post-MAIC weighted dostarlimab cohorts and the comparator in each of the MAICs are presented in Figure 33 to Figure 37.

It is clear that patients treated with dostarlimab in the GARNET trial experience a statistically significant and clinically meaningful reduction in the risk of death versus both paclitaxel and doxorubicin monotherapy; significant improvements were observed in the MAICs versus all three relevant studies.

Based on the MAIC results, patients treated with dostarlimab were approximately three times less likely to die at any given timepoint compared to patients receiving paclitaxel or doxorubicin based on McMeekin *et al.* (2015) (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]).[6] An even greater reduction in the risk of death for patients treated with dostarlimab was seen for the other two MAICs; patients treated with dostarlimab were at least five times less likely to die at any given timepoint versus patients treated with doxorubicin in Makker *et al.* (2013) (HR: [redacted]; 95% CI:[redacted], [redacted]; p<[redacted]) and Julius *et al.* (2013) (HR: [redacted]; 95% CI:[redacted], [redacted]; p<[redacted]).[7, 11] The point estimates versus Makker *et al.* (2013) and Julius *et al.* (2013) must be interpreted with caution, given the limitations associated with the MAICs; although the magnitude of the benefits observed, and their similarity to the more robust MAIC versus McMeekin et al. (2015) indicates it is likely that dostarlimab provides a significant and substantial OS benefit versus doxorubicin monotherapy and paclitaxel monotherapy.[6, 7, 11]

The HRs from the OS MAICs versus Rubinstein *et al.* (2019) and Mazgani *et al.* (2008) indicate that there are no significant differences between dostarlimab and carboplatin plus paclitaxel with respect to OS.[59, 60] However, it is important to note that the MAIC versus Rubinstein *et al.* (2019) violates the proportional hazards assumption, meaning the HR is associated with uncertainty; the sample size was too small (N=[redacted]) to estimate time varying hazards.[59] The KM curves presented in Figure 36 and Figure 37 suggest that dostarlimab may provide an increased long-term OS

benefit versus carboplatin plus paclitaxel, with evidence of a OS plateau for dostarlimab when approximately [redacted]% of patients are still alive, while the corresponding plateaus for carboplatin plus paclitaxel are associated with much lower proportions of patients alive ([redacted]% and [redacted]%, respectively).

However, considering the wide CIs, limited sample sizes (N=20 and N=31 for Rubinstein *et al.* [2019] and Mazgani *et al.* [2008], respectively) and the paucity of data on prognostic variables, it is extremely difficult to draw any meaningful conclusions about the relative benefit of dostarlimab versus carboplatin plus paclitaxel.[59, 60] The discordance in the median OS estimates in the two published studies adds further uncertainty, with estimates of 27.0 months (95% CI: 6.0, 117.0) for Rubinstein *et al.* (2019) and 15.0 months (95% CI: 9.1, 30.4) for Mazgani *et al.* (2008), respectively.[59, 60] It is clear the populations of the two studies are not homogenous, although without further details on patient characteristics and prognostic variables, it is difficult to determine if either of these populations are closely matched to the population in GARNET after the matching process.

Table 30: OS for dostarlimab versus chemotherapy comparators based on MAICs

Comparator	Reference (author, year)	MAIC comparison	
		HR (95% CI)	p-value
Paclitaxel or doxorubicin	McMeekin *et al.* (2015)[6]	[redacted]	[redacted]
Doxorubicin	Makker *et al*. (2013)[11]	[redacted]	[redacted]
PLD	Julius *et al*. (2013)[7]	[redacted]	[redacted]
Carboplatin plus paclitaxel	Rubinstein *et al.* (2019)[59]	[redacted]	[redacted]
Carboplatin plus paclitaxel	Mazgani *et al.* (2008)[60]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; PLD: pegylated liposomal doxorubicin.
Source: GSK Data on File.[13]

Figure 33: MAIC OS KM curves for dostarlimab versus paclitaxel *or* doxorubicin[a] based on McMeekin *et al.* (2015)[6]

[redacted]

Footnote: Patients in McMeekin *et al. (*2015)[6] received either paclitaxel or doxorubicin.
Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival.
Source: GSK Data on File.[13]

Figure 34: MAIC OS KM curves for dostarlimab versus doxorubicin based on Makker *et al.* (2013)[11]

Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival.
Source: GSK Data on File.[13]

Figure 35: MAIC OS KM curves for dostarlimab versus PLD based on Julius *et al.* (2013)[7]

Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival; PLD: pegylated liposomal doxorubicin.
Source: GSK Data on File.[13]

Figure 36: MAIC OS KM curves for dostarlimab versus carboplatin plus paclitaxel based on Rubinstein *et al.* (2019)[59]

Footnotes: It is likely that the MAIC between dostarlimab and carboplatin plus paclitaxel based on Rubinstein *et al.* (2019) violates the proportional hazards assumption (further detailed in Appendix D.5.3), although it is difficult to say this definitively due to the small number of patients include in Rubinstein *et al.* (2019).[59] Nonetheless, there are no viable alternatives to the proportional hazards assumption, as Rubinstein *et al.* (2019) does not report sufficient data to be able to estimate time varying hazard ratios.[59]
Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival.
Source: GSK Data on File.[13]

Figure 37: MAIC OS KM curves for dostarlimab versus carboplatin plus paclitaxel based on Mazgani *et al.* (2008)[60]

Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival.
Source: GSK Data on File.[13]

B.2.7.2.3 Strengths, limitations and conclusions of the supportive comparative efficacy evidence

ITC between dostarlimab (GARNET) and doxorubicin (ZoptEC)

Strengths and limitations of the ITC versus ZoptEC (Section B.2.7.2.1)

One of the key strengths of the comparison versus ZoptEC (relative to the MAICs versus the published studies), is that IPD was available for the ZoptEC trial.[8-10] This provided far more detailed data on patient characteristics and key prognostic factors, as well as allowing patients to be removed from both cohorts, rather than just GARNET, in order to minimise the heterogeneity between the two study populations.

Despite this, some data were still missing for patients in ZoptEC, including the number of lines of prior anti-cancer treatment, a key prognostic variable identified by clinical experts, which does limit the robustness of the comparison. However, it is important to reiterate that far more data for the patients in ZoptEC were available relative to the studies included in the MAICs, and as such, the resulting comparison in this analysis is more robust, and associated with much less uncertainty because the two populations can be more closely aligned with respect to key prognostic variables, relative to the MAICs (and particularly the MAICs versus studies other than McMeekin *et al.* [2015]).[6, 8-10]

Similar to McMeekin *et al.* (2015), ZoptEC provides a far greater sample size, including N=233 patients treated with doxorubicin monotherapy, which reduces the uncertainty associated with the comparison.[6, 8-10] This sample size is more than ten times the number of patients included in the MAICs versus Mazgani *et al.* (2008), Rubinstein *et al.* (2019) and Makker *et al.* (2008), representing another key strength of this analysis.[11, 59, 60]

Strengths and limitations of the MAICs (Section B.2.7.2.2)

The comparison between GARNET and McMeekin *et al.* (2015)[6] is the strongest comparison within this series of MAICs, and provides a reasonably robust comparison between dostarlimab and doxorubicin or paclitaxel monotherapy. McMeekin *et al.* (2015)[6] is the only RCT of the five comparator studies, and reports the most detailed inclusion/exclusion criteria and published patient characteristics and prognostic data. The inclusion/exclusion criteria are closely aligned with those of GARNET, and notably, patients with and ECOG PS of 2 were excluded from both studies.

Additionally, the detailed patient characteristics reported by McMeekin *et al.* (2015)[6] allowed for the IPD in the GARNET trial to be adjusted at a greater length, in order to align the data as closely as possible with McMeekin *et al.* (2015) [6] and to minimise any heterogeneity between the two studies before the comparison was conducted.

The robustness of the MAIC between GARNET and McMeekin *et al.* (2015)[6] was supported by a novel quasi-validation analysis, which showed a high level of agreement between the published and the MAIC-calculated endpoint estimates, with no indication of bias (this validation is detailed further in Appendix D.5.3). As a result, the comparison between dostarlimab based on GARNET and paclitaxel or doxorubicin based on McMeekin *et al.* (2015)[6] can be considered to be reasonably robust, and is associated with minimal uncertainty.

However, the MAICs between GARNET and the remaining four comparator studies must be interpreted with much more caution, and are associated with substantial uncertainty. All of these are retrospective, single-arm studies, and the lack of intra-trial randomisation means that the MAICs cannot account for any prognostic variable imbalances that are not reported, introducing an unknown level of bias. This is a concern given the paucity of reported patient characteristics and prognostic variables for these studies. Clinical expert opinion stated that the number of lines of anti-cancer treatment, histology and ECOG PS were the three most important prognostic variables that should be considered when conducting the series of MAICs. A key limitation is therefore that none of the studies (including McMeekin *et al.* [2015][6]) reported the number of lines of prior anti-cancer therapy, the most important prognostic variable.

Nevertheless, McMeekin *et al.* (2015) and Makker *et al.* (2013) did both report data on histology and ECOG PS, which experts indicated were the second and third most important prognostic

variables that should be considered.[6, 11] However, ECOG PS data was not reported by Rubinstein et al. (2019), Mazgani et al. (2008) or Julius et al. (2013), and Julius et al. (2013) did not report any information on histology.[7, 59, 60] As such, the MAICs versus Julius *et al.* (2013), Rubinstein *et al.* (2019) and Mazgani *et al.* (2008) must be interpreted with particular caution, because they may be influenced by unknown levels of bias and the GARNET population cannot be matched with respect to multiple key prognostic variables.[59, 60]

The discordance in the PFS and OS results reported in Rubinstein *et al.* (2019) and Mazgani *et al.* (2008) highlights the concern resulting from the limited information of prognostic variables.[59, 60] The clear difference in the median OS estimates of 27.0 months (95% CI: 6.0, 117.0) for Rubinstein *et al.* (2019) and 15.0 months (95% CI: 9.1, 30.4) for Mazgani *et al.* (2008) indicates that there is heterogeneity between these two populations, although the limited patient characteristics means it is difficult to know if either of these patient populations can be closely matched to the GARNET trial as part of the matching process.[59, 60]

The sample sizes of these studies represents a further limitation. Aside from McMeekin *et al.* (2015)[6], the largest of the other four studies, Julius *et al.* (2013), only included 41 patients in the relevant study population, while the relevant populations of Rubinstein *et al.* (2019), Mazgani *et al.* (2008) and Makker *et al.* (2013) included 20, 19 and 17 patients, respectively.[7, 11, 59, 60] These extremely small sample sizes mean that all of the resulting MAICs, and point estimates (HRs), are highly unreliable and must be interpreted with caution. The small sample sizes result in a further limitation for the MAICs versus Rubinstein *et al.* (2019); the proportional hazards assumption was violated for both PFS and OS meaning that the HRs are associated with substantial uncertainty, although, due to the small sample size, it is not possible to account for this by estimating time-varying HRs.[59]

Conclusions

The results of the IPTW ITC versus doxorubicin monotherapy based on the ZoptEC study provide clear evidence of the marked survival benefit of dostarlimab compared to doxorubicin monotherapy.[8-10] The comparison estimates that patients treated with dostarlimab were [redacted]% less likely to die at any given timepoint compared to patients receiving doxorubicin monotherapy (HR: [redacted]; 95% CI: ([redacted], [redacted]); p[redacted]).The results of the MAIC versus McMeekin *et al.* (2015)[6] suggest that dostarlimab provides an even greater OS benefit, indicating that patients were [redacted] less likely to die at any given timepoint compared to patients receiving paclitaxel or doxorubicin monotherapy (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]).

These two comparisons represent the most robust analyses, and the similarity of the results suggests that it is reasonable to conclude the true magnitude of the OS benefit that dostarlimab provides relative to doxorubicin monotherapy lies approximately around a [redacted]%–[redacted]% reduced risk of death (HR: [redacted]–[redacted]) based on the OS HRs for dostarlimab versus doxorubicin monotherapy in ZoptEC, and dostarlimab versus doxorubicin or paclitaxel monotherapy in McMeekin *et al.* (2015).[6, 8-10] Clinical experts indicated it is reasonable to assume that the efficacy of paclitaxel monotherapy is approximately equal to doxorubicin monotherapy, and so the OS benefit for dostarlimab versus paclitaxel is likely to be similar.

It is more difficult to draw any meaningful conclusions versus the remaining four MAICs, due to the substantial limitations and associated uncertainty. The MAICs versus Makker *et al*. (2013) and Julius *et al.* (2013) both suggest that dostarlimab provides an even greater OS benefit versus doxorubicin monotherapy, compared to the results observed in the MAICs versus ZoptEC

and McMeekin *et al.* (2015).[6-10] The exact magnitude of the benefits observed in the MAICs versus Makker *et al.* (2013) and Julius *et al.* (2013) are highly uncertain, but the magnitude of these risk reductions favour dostarlimab to such a degree that it would be extremely unlikely that any prognostic imbalances that could not be accounted for would eliminate this advantage completely.[7, 11] Therefore, it can be concluded that these MAICs provide additional supportive evidence for an OS benefit for dostarlimab versus doxorubicin monotherapy, despite the associated uncertainty.

Similarly, the MAICs versus Rubinstein *et al.* (2019) and Mazgani *et al.* (2008) are associated with substantial uncertainty.[59, 60] These MAICs indicate that there are no significant differences between dostarlimab and carboplatin plus paclitaxel with respect to PFS or OS, although, the limitations noted previously mean that the analyses are insufficiently robust to draw conclusions with any certainty.

The results of the ITCs versus the published literature presented in this section were considered within economic scenario analyses, in order to provide supportive evidence to the base case economic analysis comparison versus the UK RWE study, as detailed in Section B.3.8.3.

B.2.7.3 Comparative efficacy evidence versus hormone therapy

Hormone therapy was not fully captured within the UK RWE study, because this study only included treatments captured within the SACT dataset, which primarily focusses on treatments provided in secondary care. Patients receiving hormone therapy dispensed in primary care or community pharmacies would therefore not have been captured in this analysis.

Hormone therapies were also not included in the original clinical SLR, because they were not considered to be relevant comparators to dostarlimab in this submission at the time the review of conducted. However, hormone therapy has since been included in the NICE final scope for this submission, and UK clinical expert opinion sought by GSK has since suggested that hormone therapies, specifically medroxyprogesterone acetate and letrozole, may also be treatment options for a patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy. These patients may be treated with hormone therapy despite the fact that BGCS guidelines highlight that there is no evidence that hormone therapy confers any survival benefit in the post-platinum setting.[14] In order to identify any relevant published evidence for hormone therapies in this indication, a targeted literature review (detailed in Appendix L) was conducted. The review followed the same eligibility criteria of the clinical SLR but was limited to searches of PubMed, which comprises more than 30 million citations from MEDLINE, life science journal and online books.

The targeted literature review did not identify any studies that provided evidence for hormone therapies in the correct population relevant to this submission's decision problem: i.e. patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy. Consequently, in order to attempt a possible direct comparison between dostarlimab and hormone therapy, the studies that were excluded at the full-text review stage of the targeted literature review were re-evaluated using a relaxed set of eligibility criteria to try and identify any published PFS and OS data.

The process of identifying potential studies for inclusion, and a summary of the six studies that were included as part of this re-evaluation, is provided in Appendix L.5. The patients in these six studies did not represent a GARNET-like population, but the possibility of using these studies as

a potentially relevant proxy to inform a comparison between dostarlimab and hormone therapy was explored.

However, UK clinical experts strongly indicated that they did not consider these studies to represent a plausible proxy for hormone therapy for patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy. The substantial heterogeneity between the patient populations in these studies and the patient population in GARNET meant that the median survival outcomes reported in these studies were not considered to be reflective of the survival outcomes that would be associated with hormone therapy in the post-platinum setting.

Based on the recommendations from UK clinical experts, it was concluded that any comparisons between GARNET and these studies would be associated with too much uncertainty to be meaningful. Ultimately, it was therefore not possible to conduct any clinical efficacy comparison between dostarlimab and hormone therapy in this submission. A scenario analysis was conducted assuming that hormone therapy as equal to the efficacy of current clinical management (Section B.3.8.3).

B.2.8 Adverse reactions

Safety profile of dostarlimab

- In GARNET, dostarlimab was shown to be well-tolerated, and associated with a manageable adverse event (AE) profile – treatment related treatment-emergent adverse events (TEAEs) were generally low grade (only [redacted]% of patients reported any Grade ≥3 treatment-related TEAE), and discontinuation as a result of treatment-related AEs was low ([redacted]%).
- The most frequent treatment-related TEAEs were diarrhoea ([redacted]%), asthenia ([redacted]%), fatigue ([redacted]%) and nausea ([redacted]%). In total, [redacted] patients experienced a ≥ Grade 3 treatment-related TEAE; the most frequently observed events were anaemia in [redacted] patients ([redacted]%) and lipase increased in [redacted] patients ([redacted]%).
- Treatment-related serious TEAEs were experienced by [redacted] patients ([redacted]%). Colitis was the only treatment-related serious TEAE reported in more than one patient ([redacted] patients [[redacted]%]). No deaths were associated with dostarlimab.

Dostarlimab versus current clinical management

- Cytotoxic chemotherapy regimens are associated with debilitating side effects and a substantial burden of toxicity to patients. In the ZoptEC study, 96.4% of patients receiving doxorubicin monotherapy study reported a treatment-related TEAE (compared to [redacted]% in GARNET), and [redacted]% of patients reported any Grade >3 TEAE in ZoptEC (versus [redacted]% in GARNET).[8-10]
- The variety in types and frequency of treatment-related TEAEs also highlight the increased burden of toxicity of chemotherapy relative to dostarlimab. The main differences observed between dostarlimab and doxorubicin monotherapy in the ZoptEC study include anaemia ([redacted]% versus 40.6% in GARNET and ZoptEC, respectively), fatigue ([redacted]% versus 39.8%) and nausea ([redacted]% versus 50.2%).[8-10]
- Alopecia and neutropenia were not reported as frequently observed TEAEs experienced by [redacted]% of patients in the GARNET study, while 34.9% and 50.6% of patients in ZoptEC experienced alopecia and neutropenia, respectively.[8-10]

Summary

- Overall, the safety data suggest that the AE profile of dostarlimab is aligned with other currently licensed anti-PD-L1 therapies, and no unexpected AE signals were identified.
- Alongside the potential efficacy benefit that dostarlimab may provide, it is clear that dostarlimab is associated with a reduced burden of toxicity versus cytotoxic chemotherapy regimens that are currently used in UK clinical practice.

In the GARNET study, the safety profile of dostarlimab was evaluated based on reported AEs, which were captured as a secondary endpoint. Safety data are presented for the safety analysis set which was defined as all patients who received any amount of dostarlimab regardless of follow-up time at the time of IA2 (DCO 1st March 2020) (Table 8) (N=129). As the safety analysis set represents the same patient population as the ITT population, it is hereafter referred to as the ITT population.

Overall, dostarlimab was shown to be well-tolerated. The majority of treatment-related TEAEs were of low grade; only [redacted]% of patients reported any Grade ≥3 treatment-related TEAE. Discontinuation as a result of treatment-related AEs was low ([redacted]%). Overall, the safety data suggest that the AE profile of dostarlimab is aligned with other currently licensed anti-PD-L1 I-O therapies, and with no unexpected AE signals identified at the time of IA2 (DCO 1st March 2020).

B.2.8.1 Treatment exposure

A total of 129 patients had received at least one dose of dostarlimab and were included in the safety analysis at the time of IA2 (DCO: 1st March 2020). The overall median treatment duration was [redacted] weeks (range: [redacted] weeks), and the mean was [redacted] weeks (STD: [redacted]).

In total, [redacted] patients ([redacted]%) were exposed to dostarlimab monotherapy for at least 24 weeks, whereas [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%) were exposed for at least 48 and 72 weeks respectively. The median treatment dose intensity of [redacted]% indicates that the majority of patients in GARNET received treatment as planned, without delays or interruptions.

A detailed overview on the duration of treatment with dostarlimab is provided in Table 31.

Table 31: Duration of treatment with dostarlimab (ITT population)

Treatment by cycle in weeks, n (%)	ITT population (N=129)
Week 1 – ≤ Week 3	[redacted]
Week 4 – ≤ Week 6	[redacted]
Week 7 – ≤ Week 9	[redacted]
Week 10 – ≤ Week 12	[redacted]
Week 13 – ≤ Week 18	[redacted]
Week 19 – ≤ Week 24	[redacted]
Week 25 – ≤ Week 30	[redacted]
Week 31 – ≤ Week 36	[redacted]
Week 37 – ≤ Week 42	[redacted]
Overall duration of treatment (weeks)	
N	[redacted]
Mean (STD)	[redacted]

Median	[redacted]
IQR	[redacted]
Min, Max	[redacted]
Dose intensity	
Median dose intensity	[redacted]

Abbreviations: IQR: interquartile range; ITT: intention to treat; STD: standard deviation.
Source: GSK Data on File.[54]

B.2.8.2 TEAEs

TEAEs were defined per protocol as any AE or serious adverse event (SAE) with onset beginning at the day of first administration of study treatment, throughout the treatment period until 90 days after the EOT visit (or until the start of alternate anticancer therapy, whichever occurred earlier), or any event that was present at baseline but worsened in intensity or was subsequently considered treatment-related by the Investigator through the end of the study.

Most patients in the ITT population (N=129) experienced at least 1 TEAE ([redacted]%; Table 32). Treatment-related TEAEs were reported in [redacted]% of patients. The majority of TEAEs were not severe or serious and did not require treatment interruption or discontinuation. TEAEs leading to death were reported in [redacted] patients ([redacted]%); none of these TEAEs were assessed by the Investigator as related to study treatment or considered to be an immune-related adverse event (irAE).

A summary of TEAEs in GARNET is presented in Table 32.

Table 32: Overall summary of TEAEs (ITT population)

Category, n (%)	ITT population (N=129)
Any TEAEs	[redacted]
Any Grade ≥3 TEAEs	[redacted]
Any TEAEs leading to death	[redacted]
Any serious TEAEs	[redacted]
Any TEAEs leading to permanent treatment discontinuation	[redacted]
Any TEAE leading to study treatment interruption	[redacted]
Any irAE	[redacted]
Any dostarlimab infusion-related reactions	[redacted]

Footnotes: For each category, participants were included only once, even if they experienced multiple events in that category. TEAEs are new AEs that began, or any pre-existing condition that worsened in severity, after at least 1 dose of study treatment was administered and throughout the treatment period until 90 days after the EOT Visit (or until the start of alternate anticancer therapy, whichever occurred earlier). AE severity was graded using NCI CTCAE v4.03.
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EOT: end-of-treatment; irAE: immune-related adverse event; ITT: intention to treat; NCI: National Cancer Institute; TEAE: treatment-emergent adverse event.
Source: GSK Data on File.[13]

The most frequently reported TEAEs (≥20%) with dostarlimab were [redacted], [redacted], [redacted], [redacted], and [redacted]. These common TEAEs were Grade 1 or Grade 2 in severity in most patients for whom the TEAEs were reported, with the exception of [redacted], for which [redacted] patients ([redacted]%) had Grade 3 events. A summary of common TEAEs (≥10% of patients) is presented in Table 33.

Table 33: Common TEAEs by system organ class and preferred term (≥10% of patients) (ITT population)

System organ class; Preferred term, n (%)	ITT population (N=129)
Any TEAEs	[redacted]
General disorders and administration site conditions	[redacted]
Fatigue	[redacted]
Asthenia	[redacted]
Pyrexia	[redacted]
Oedema peripheral	[redacted]
Gastrointestinal disorders	[redacted]
Nausea	[redacted]
Diarrhoea	[redacted]
Constipation	[redacted]
Vomiting	[redacted]
Abdominal pain	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]
Arthralgia	[redacted]
Back pain	[redacted]
Myalgia	[redacted]
Infections and infestations	[redacted]
Urinary tract infection	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]
Cough	[redacted]
Metabolism and nutrition disorders	[redacted]
Decreased appetite	[redacted]
Skin and subcutaneous tissue disorders	[redacted]
Pruritus	[redacted]
Rash	[redacted]
Blood and lymphatic system disorders	[redacted]
Anaemia	[redacted]

Footnotes: AEs were coded using MedDRA version 23.0. For each preferred term, a patient was included only once, even if they experienced multiple events in that preferred term. TEAEs are new AEs that began, or any pre-existing condition that worsened in severity, after at least one dose of study treatment was administered and throughout the treatment period until 90 days after the EOT Visit (or until the start of alternate anti-cancer therapy, whichever occurred earlier).
Abbreviations: AE: adverse event; EOT: end-of-treatment; ITT, intention-to-treat; MedDRA: Medical Dictionary for Regulatory Activities; TEAE: treatment-emergent adverse event.
Source: GSK Data on File.[13]

Grade ≥3 TEAEs were reported in [redacted] patients ([redacted]%). The Grade ≥3 TEAEs with the highest incidence (≥5%) were [redacted] and [redacted]. A summary of Grade 3 or greater TEAEs occurring in more than three patients is presented in Table 34.

Table 34: Grade 3 or greater TEAEs occurring in ≥3 patients (ITT population)

Category, n (%)	ITT population (N=129)
Any Grade ≥3 TEAE	[redacted]

Grade 3 Anaemia	[redacted]
Grade 3 Abdominal pain	[redacted]
Hyponatraemia	[redacted]
Grade 3	[redacted]
Grade 4	[redacted]
Grade 3 Acute kidney injury	[redacted]
Grade 3 Back pain	[redacted]
Pulmonary embolism	[redacted]
Grade 3	[redacted]
Grade 4	[redacted]
Sepsis	[redacted]
Grade 4	[redacted]
Grade 5	[redacted]
Grade 3 Alanine aminotransferase increased	[redacted]
Grade 3 Diarrhoea	[redacted]
Grade 3 Hypertension	[redacted]
Grade 3 Lipase increased	[redacted]
Pneumonia	[redacted]
Grade 3	[redacted]
Grade 5	[redacted]
Grade 3 Urinary tract infection	[redacted]

Footnotes: AEs were coded using MedDRA version 23.0. AE severity was graded using NCI CTCAE v4.03. For each preferred term, a patient was included only once, even if they experienced multiple events in that preferred term. TEAEs are new AEs that began, or any pre-existing condition that worsened in severity, after at least one dose of study treatment was administered and throughout the treatment period until 90 days after the EOT Visit (or until the start of alternate anti-cancer therapy, whichever occurred earlier).
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EOT: end-of-treatment; ITT: intention-to-treat; MedDRA: Medical Dictionary for Regulatory Activities; NCI: National Cancer Institute; TEAE: treatment-emergent adverse event.
Source: GSK Data on File.[54]

The only Grade 4 TEAE reported in >1% of patients was [redacted] ([redacted] patients [redacted%]). Grade 4 TEAEs of [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] were reported in [redacted] patient ([redacted%]) each. Grade 5 TEAEs of [redacted], [redacted], [redacted], [redacted], and [redacted] were reported in [redacted] patient ([redacted%]) each. None of the Grade 5 TEAEs were considered related to study treatment by the Investigator.

In total, [redacted] patients experienced TEAEs leading to study treatment interruption; the most frequently reported TEAEs leading to treatment interruptions (>2% of patients) were [redacted] and [redacted]. A total of [redacted] patients ([redacted%]) experienced TEAEs that led to discontinuation of study treatment. [redacted] and [redacted] were the only TEAEs reported in >1 patient that led to permanent discontinuation of study treatment ([redacted] patients [redacted%] each, all events were Grade 3).

It is important to note that Grade ≥3 irAEs of alanine aminotransferase increase, aspartate aminotransferase increased, and pneumonitis required permanent discontinuation of study treatment per protocol.

B.2.8.3 Treatment-related TEAEs

A total of [redacted] of 129 patients ([redacted]%) experienced a treatment-related TEAE. Treatment-related TEAEs experienced by patients treated with dostarlimab were generally low grade, and characteristic of anti-PD-1 therapy. A summary of treatment-related TEAEs is presented in Table 37.

Table 35: Overall summary of treatment-related TEAEs (ITT population)

Category, n (%)	ITT population (N=129)
Any treatment-related TEAEs	[redacted]
Any Grade ≥3 treatment-related TEAEs	[redacted]
Any treatment-related TEAEs leading to death	[redacted]
Any treatment-related serious TEAEs	[redacted]
Any treatment-related TEAEs leading to permanent treatment discontinuation	[redacted]
Any treatment-related irAE	[redacted]

Footnotes: For each category, participants were included only once, even if they experienced multiple events in that category. TEAEs are new AEs that began, or any pre-existing condition that worsened in severity, after at least 1 dose of study treatment was administered and throughout the treatment period until 90 days after the EOT Visit (or until the start of alternate anticancer therapy, whichever occurred earlier). AE severity was graded using NCI CTCAE v4.03.
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EOT: end-of-treatment; irAE: immune-related adverse event; ITT: intention-to-treat; MedDRA: Medical Dictionary for Regulatory Activities; NCI: National Cancer Institute; TEAE: treatment-emergent adverse event.
Source: GSK Data on File.[54]

The most frequently reported treatment-related TEAEs (occurring in ≥5% of patients) were diarrhoea ([redacted]%), asthenia ([redacted]%), fatigue ([redacted]%), nausea ([redacted]%), pruritus ([redacted]%), arthralgia ([redacted]%), hypothyroidism ([redacted]%), anaemia ([redacted]%) and rash ([redacted]%). A summary of treatment-related TEAEs occurring in ≥5% of patients is presented in Table 36.

Table 36: Treatment-related TEAEs experienced by ≥5% of patients (ITT population)

Category, n (%)	ITT population (N=129)
Any treatment-related TEAEs	[redacted]
Diarrhoea	[redacted]
Asthenia	[redacted]
Fatigue	[redacted]
Nausea	[redacted]
Arthralgia	[redacted]
Pruritus	[redacted]
Anaemia	[redacted]
Hypothyroidism	[redacted]
Rash	[redacted]

Footnotes: AEs were coded using MedDRA version 23.0. For each preferred term, a patient was included only once, even if they experienced multiple events in that preferred term. TEAEs are new AEs that began, or any pre-existing condition that worsened in severity, after at least one dose of study treatment was administered and throughout the treatment period until 90 days after the EOT Visit (or until the start of alternate anti-cancer therapy, whichever occurred earlier).
Abbreviations: AE: adverse event; EOT: end-of-treatment; MedDRA: Medical Dictionary for Regulatory Activities; ITT: intention to treat; TEAE: treatment-emergent adverse event.
Source: GSK Data on File.[54]

Treatment-related Grade ≥3 TEAEs were experienced by [redacted] patients ([redacted]%). Anaemia ([redacted] patients [[redacted]%]) and lipase increased ([redacted] patients [[redacted]%]) were the only treatment-related Grade ≥3 TEAEs reported in >2 patients. Table 37 shows related Grade 3 and above treatment-related TEAEs that occurred in 2 or more patients.

Table 37: Treatment-related[a] Grade ≥3 TEAEs occurring in ≥2 patients (ITT population)

AE preferred term, n (%)	ITT population (N=129)
Any Grade ≥3 treatment-related TEAEs	[redacted]
Any Grade 3 treatment-related TEAEs	[redacted]
Any Grade 4 treatment-related TEAEs	[redacted]
Any Grade 5 treatment-related TEAEs	[redacted]
Grade 3 anaemia	[redacted]
Grade 3 lipase increased	[redacted]
Grade 3 alanine aminotransferase increased	[redacted]
Grade 3 colitis	[redacted]
Grade 3 diarrhoea	[redacted]
Grade 3 transaminases increased	[redacted]

Footnotes: AEs were coded using MedDRA version 23.0. AE severity was graded using NCI CTCAE v4.03. For each preferred term, a patient was included only once, even if they experienced multiple events in that preferred term. TEAEs are new AEs that began, or any pre-existing condition that worsened in severity, after at least one dose of study treatment was administered and throughout the treatment period until 90 days after the EOT Visit (or until the start of alternate anti-cancer therapy, whichever occurred earlier). Treatment-related TEAEs refer to any TEAE assessed by the Investigator as related to study treatment ("Related, "Possibly Related" or missing). Events are summarised according to the maximum CTCAE grade experienced by the patient for that event.
Abbreviations: AE: adverse event; ALT: alanine aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; EOT: end-of-treatment; ITT: intention to treat; MedDRA: Medical Dictionary for Regulatory Activities; NCI: National Cancer Institute; TEAE: treatment-emergent adverse event.
Source: GSK Data on File.[54]

B.2.8.4 Serious TEAEs

Serious TEAEs were experienced by [redacted] patients ([redacted]%) in the ITT population. The most frequently reported serious TEAEs (>2%) were [redacted], [redacted], [redacted], [redacted], [redacted] and [redacted]. Table 38 presents details of serious TEAEs experienced by >1% of patients.

Table 38: Serious TEAEs by system organ class and preferred term experienced by >1% of patients (ITT population)

Category, n (%)	ITT population (N=129)
Patients with at least 1 serious TEAE	[redacted]
Gastrointestinal disorders	[redacted]
Abdominal pain	[redacted]
Colitis	[redacted]
Intestinal obstruction	[redacted]
Infections and infestations	[redacted]
Sepsis	[redacted]
Urinary tract infection	[redacted]
Bronchitis	[redacted]
Pneumonia	[redacted]

Pyelonephritis	[redacted]
General disorders and administration site conditions	[redacted]
Pyrexia	[redacted]
General physical health deterioration	[redacted]
Pain	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]
Pulmonary embolism	[redacted]
Renal and urinary disorders	[redacted]
Acute kidney injury	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]
Tumour pain	[redacted]

Footnotes: AEs were coded using MedDRA version 23.0. For each preferred term, a patient was included only once, even if they experienced multiple events in that preferred term. TEAEs are new AEs that began, or any pre-existing condition that worsened in severity, after at least one dose of study treatment was administered and throughout the treatment period until 90 days after the EOT Visit (or until the start of alternate anticancer therapy, whichever occurred earlier). SAEs between the first dose date and 90 days after the EOT Visit are summarised.
Abbreviations: EOT: end-of-treatment; ITT: intention-to-treat; MedDRA: Medical Dictionary for Regulatory Activities; TEAE: treatment-emergent adverse event.
Source: GSK- Data on File.[13]

B.2.8.5 Treatment-related serious TEAEs

Treatment-related serious TEAEs were experienced by [redacted] patients ([redacted]%). [redacted] was the only treatment-related serious TEAE reported in >1 patient ([redacted] patients [[redacted]%]). A list of treatment-related serious TEAEs is presented in Table 39.

Table 39: Treatment-related serious TEAEs (ITT population)

Category, n (%)	ITT population (N=129)
Any treatment-related serious TEAE	[redacted]
Colitis	[redacted]
Asthenia	[redacted]
Constipation	[redacted]
Iridocyclitis	[redacted]
Myalgia	[redacted]
Pancreatitis	[redacted]
Pancreatitis acute	[redacted]
Pemphigoid	[redacted]
Pneumonitis	[redacted]
Pulmonary embolism	[redacted]
Pyrexia	[redacted]
Transaminases increased	[redacted]
Tubulointerstitial nephritis	[redacted]

Footnotes: AEs were coded using MedDRA version 23.0. For each preferred term, a patient was included only once, even if they experienced multiple events in that preferred term. TEAEs are new AEs that began, or any pre-existing condition that worsened in severity, after at least one dose of study treatment was administered and throughout the treatment period until 90 days after the EOT Visit (or until the start of alternate anticancer therapy, whichever occurred earlier). Serious TEAEs between the first dose date and 90 days after last dose date are

summarised. Treatment-related TEAEs refer to any TEAE assessed by the Investigator as related to study treatment ("Related," "Possibly Related," or missing).
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EOT: end-of-treatment; ITT: intention-to-treat; MedDRA: Medical Dictionary for Regulatory Activities; NCI: National Cancer Institute; TEAE: treatment-emergent adverse event.
Source: GSK Data on File.[54]

B.2.8.6 Deaths

A total of [redacted] patients ([redacted]%) died while in the study. Overall, the most common primary reason for death was disease progression.

Of the [redacted] patients with who died while in the study, [redacted] patients had a treatment-unrelated TEAE leading to death. All TEAEs leading to death ([redacted], [redacted], [redacted], [redacted], and [redacted]) were reported in [redacted] patient each. Of all [redacted] TEAEs leading to death, [redacted] each were classed as System Organ Classes (SOCs) of '[redacted]', '[redacted]', '[redacted]', and '[redacted]', respectively. None of the TEAEs that led to death were assessed by the Investigator as related to dostarlimab or considered to be an irAE. A summary of the deaths in GARNET is presented in Table 40.

Table 40: Summary of deaths in GARNET (ITT population)

Category, n (%)	ITT population (N=129)
During the treatment period[a]	
Deaths	[redacted]
Progressive disease	[redacted]
AE	[redacted]
During the 90-day safety follow-up period[b]	
Deaths	[redacted]
Progressive disease	[redacted]
AE	[redacted]
During the long-term follow-up period[c]	
Deaths	[redacted]
Progressive disease	[redacted]

Footnotes: [a] If the last cycle of treatment was ≤4 cycles, the duration of treatment was from first dose to last dose of dostarlimab +21 days; otherwise, it was from first dose to last dose of dostarlimab +42 days. [b] Within 90 days after the EOT Visit or until the first follow-up anticancer therapy, whichever occurred earlier. [c] After the EOT Visit +90 days or until the first follow-up anticancer therapy, whichever occurred earlier.
Abbreviations: AE: adverse event; EOT: end-of-treatment; ITT: intention-to-treat.
Source: GSK Data on File.[54]

B.2.8.7 Comparative safety

Unfortunately, no AE information is available in the NCRAS data set, therefore safety data were not captured in the UK RWE study. Consequently, naïve comparisons of the safety of dostarlimab versus current clinical management from studies identified in the clinical SLR are discussed below.

It is important to note that comparisons of safety and AEs between studies must be interpreted with caution, because trial designs and the protocol for AEs reporting and classification may be different between studies.

Of the relevant studies identified in the clinical SLR for individual comparator chemotherapy regimens, only a few reported any details on the safety profile of the chemotherapies listed in the NICE final scope. Studies reporting safety and tolerability information included Lincoln *et al.* (2003) (paclitaxel monotherapy), McMeekin *et al.* (2015)[6] (paclitaxel or doxorubicin monotherapy) and the ZoptEC study (doxorubicin monotherapy).[8-10]

Despite the paucity of AE data, it is apparent that patients treated with dostarlimab experience a reduced burden of toxicity relative to patients receiving chemotherapy. Overall, [redacted]% of patients receiving dostarlimab in GARNET experienced any treatment-related TEAEs; in comparison, 90% of patients receiving paclitaxel or doxorubicin monotherapy in McMeekin *et al.* (2015)[6], and almost all of the patients receiving doxorubicin monotherapy in ZoptEC (96.4%) experienced a treatment-related TEAE.[8-10] Similarly, only [redacted]% of patients experienced a Grade≥3 treatment-related TEAE in GARNET, compared to over half of the patients receiving paclitaxel monotherapy in Lincoln *et al.* (2003) (58.3%).

A summary of the treatment-related TEAE data presented for patients receiving dostarlimab in GARNET and patients in the chemotherapy studies in presented in Table 41, though it should be noted that these comparisons are naïve only.

Table 41: Summary of treatment-related TEAEs in dostarlimab versus chemotherapy studies identified in the clinical SLR (naïve comparisons only)

Trial	GARNET ITT population (N=129)	Lincoln *et al.* (2003)[49] (N=48)	ZoptEC[8-10] (N=249)	McMeekin *et al.* (2015)[6] (N=239)
Intervention	**Dostarlimab**	**Paclitaxel monotherapy**	**Doxorubicin monotherapy**	**Paclitaxel *or* doxorubicin monotherapy**
Any treatment-related TEAEs, n (%)	[redacted]	NR	240 (96.4)	215 (90.0)
Any Grade ≥3 treatment related TEAEs, n (%)	[redacted]	28 (58.3)	NR	NR
Any treatment-related SAE, n (%)	[redacted]	NR	NR	29 (12.0)

Abbreviations: ITT: intention-to-treat; NR: not reported; SAE: serious adverse event; SLR: systematic literature review; TEAE: treatment-emergent adverse event.

There was clear variety in the types and frequency of treatment-related TEAEs experienced by patients receiving dostarlimab versus patients receiving doxorubicin monotherapy in ZoptEC.[8-10] The main differences that were observed between dostarlimab and doxorubicin monotherapy include anaemia ([redacted]% versus 40.6% in GARNET and ZoptEC, respectively), fatigue ([redacted]% versus [redacted]%) and nausea ([redacted]% versus 50.2%), highlighting the increased burden of toxicity of chemotherapy relative to dostarlimab.[8-10] Moreover, alopecia and neutropenia were [redacted] as frequently observed TEAEs experienced by [redacted]% of patients in the GARNET study, while [redacted]% and [redacted]% of patients in ZoptEC experienced alopecia and neutropenia, respectively.[8-10]

A summary of treatment-related TEAEs experienced in the GARNET and ZoptEC trials is

provided in Table 42, though it should be noted that these comparisons are naïve only.[8-10]

Table 42: Treatment-related TEAEs experienced patients in GARNET and ZoptEC (naïve comparison only)[8-10]

Category, n (%)	GARNET ITT population (N=129)[a]	Patients receiving doxorubicin in ZoptEC (N=[redacted])[b]
Any treatment-related TEAEs	[redacted]	240 (96.4)
Alopecia	[redacted]	[redacted]
Anaemia	[redacted]	101 (40.6)
Arthralgia	[redacted]	NR
Asthenia	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Hypothyroidism	[redacted]	NR
Nausea	[redacted]	125 (50.2)
Neutropenia	[redacted]	126 (50.6)
Pruritus	[redacted]	NR
Rash	[redacted]	NR

Footnotes: [a] AEs in GARNET were coded using MedDRA version 23.0. For each preferred term, a patient was included only once, even if they experienced multiple events in that preferred term. TEAEs are new AEs that began, or any pre-existing condition that worsened in severity, after at least one dose of study treatment was administered and throughout the treatment period until 90 days after the EOT Visit (or until the start of alternate anti-cancer therapy, whichever occurred earlier). [b] Each AE and SAE term reported in ZoptEC was mapped to a preferred term using theMedDRA dictionary. The investigator classified the severity of AEs using the NCI CTCAE v4.03 and will assess the relationship of each event to study treatment.
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EOT: end of treatment; ITT: intention-to-treat; MedDRA: Medical Dictionary for Regulatory Activities; NCI: National Cancer Institute; NR: not reported; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: GSK Data on File.[13] ZoptEC.[8-10]

As highlighted previously, no relevant studies in the patient population of interest were identified for hormone therapy in the targeted literature review. Feedback from clinical experts indicated that the PARAGON study may provide information on the AE profile of hormone therapy and data from this study suggest hormone therapy is associated with a mild safety profile; the only Grade ≥3 AE reported in ≥5% of patients was fatigue.[74]

B.2.9 Ongoing studies

The GARNET trial is still ongoing, with the next data cut expected in early 2022. Dostarlimab is also currently being investigated as a first-line treatment in combination with carboplatin plus paclitaxel for patients with recurrent or advanced EC in the Phase III randomised RUBY trial (NCT03981796).[75] The study has an estimated primary completion date of October 11, 2021.[55]

B.2.10 Innovation

Dostarlimab is a treatment option for patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after a platinum-containing regimen. This patient population, which equates to approximately 124 women each year in England, reflects a small, well-defined proportion of the total EC population, and represents the patients with the highest unmet need.

Currently, there is no definitive standard of care for these patients, who are left feeling abandoned and facing a bleak prognosis, with extremely limited and inadequate treatments options based on unclear and inconsistent treatment guidelines (as a result of the dearth of adequate data in this area). Many patients will receive further lines of chemotherapy, although by this stage, EC is considered to be a chemotherapy-resistant disease.[12] A number of patients may alternatively receive hormone therapy, despite the fact that there are no robust published data to support the efficacy of hormone therapy in this post-platinum setting.[14] No new treatment options have been licensed in the UK for this patient population for decades and there remains a critical unmet need for a new addition to the treatment armamentarium with a novel mechanism of action.

Dostarlimab brings innovation to the treatment paradigm for patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after a platinum-containing regimen. It is the first I-O therapy to receive a licence in this indication and has an entirely novel and distinct mechanism of action to the treatment options currently available for these patients. As a humanised, monoclonal antibody, dostarlimab binds with high affinity and specificity to PD-1, a cell surface receptor expressed on activated T-cells.[19] By inhibiting the binding of PD-1 to PD-L1 and PD-L2, dostarlimab blocks the PD-1 signalling pathway and subsequent immune evasion resulting in an increased anti-tumour immune response.

Like other I-O therapies, the mechanism of action of dostarlimab enables a patient's own immune system to mount an anti-tumour response. This novel mechanism of action has allowed other I-O therapies to revolutionise the management of other cancers, including colorectal and lung cancer and melanoma, where I-O therapies have demonstrating clinically meaningful responses and significantly improved the prognosis for many patients. Most notably, I-O therapies have been shown to result in extended treatment benefits and long-term remission even after treatment discontinuation.[52]

Illustrating the unmet need, it is noted that nivolumab, which is not licensed in this setting, is currently available via the CDF for patients with metastatic or locally advanced dMMR/MSI-H EC through a COVID-19 response programme due to the belief in it having tumour agnostic properties. Nevertheless, there is no available clinical evidence to support the use of nivolumab monotherapy for advanced and recurrent endometrial cancer, nor is a license in this indication being explored to our knowledge.[16] The introduction of a licensed treatment option, such as dostarlimab, would be preferred by UK clinical experts, given the availability of regulatory-approved data when making a prescribing decision. The use of nivolumab highlights the exceptional unmet clinical need and the limited options available for patients in this setting.

dMMR/MSI-H EC is a subtype of EC that comprises approximately 23% of all ECs and represents a subgroup where dostarlimab and PD-1/PD-L1 inhibition is most effective.[18, 23] dMMR/MSI-H EC is highly immunogenic, and exhibits more tumour-specific neoantigens, which results in increased T-cells, including tumour-infiltrating lymphocytes, and compensatory upregulation of immune checkpoints.[23] This combination of increased mutation load, T-cells and

PD-1/PD-L1 expression means that dMMR/MSI-H EC represents an ideal target for dostarlimab and PD-1/PD-L1 inhibition and the efficacy of dostarlimab in this patient population has been realised in the pivotal GARNET trial.[23]

The fact that dostarlimab uses a patient's own immune system to mount an anti-tumour response also means that AEs are more likely to be on-target and dostarlimab is associated with a reduced burden of toxicity when compared to the indiscriminate cytotoxic effects of chemotherapy.[16] Chemotherapy is associated with a number of harmful and debiliating side effects, and has a substantial detrimental impact on patients with EC.[16]

The dosing schedule of dostarlimab is six-weekly versus chemotherapies which have a three to four-weekly dosing schedule.[76, 77] As such, feedback from a UK clinical expert was that the greater gap between each IV administration of dostarlimab may also substantially improve patient convenience and adherence, by reducing the number of required hospital visits.[16]

Finally, it is important to note how during the recent NICE scoping workshop, there was significant excitement about dostarlimab from both the patient group representatives and the clinical experts. GSK have received the same excitement from advisory boards and other insight seeking activities, which clearly and conclusively highlights how dostarlimab would represent a critical addition to the treatment armamentarium for EC, providing hope to patients who currently feel abandoned and who face an extremely dire prognosis with almost no chance of receiving effective treatment.

B.2.11 Interpretation of clinical effectiveness and safety evidence

B.2.11.1 Principal findings from the clinical evidence base

Overall survival

In the GARNET trial, dostarlimab demonstrated a remarkable OS benefit when compared to current clinical management in the UK. Naïve comparisons of the OS results in GARNET versus those in the UK RWE study and the published literature demonstrate that the introduction of dostarlimab would represent a clinically meaningful step-change in the management of patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or after platinum-based chemotherapy.

After 12 months of treatment with dostarlimab, [redacted]% of patients were still alive, and [redacted]% of patients were progression-free. Most notably, a clear and sustained survival benefit was observed; by Month 24, [redacted]% of patients were still alive, and [redacted]% of patients were still progression-free.

These results paint current clinical management in harrowing light, with the UK RWE study showing that just [redacted]% of patients were alive at Month 12. Unlike GARNET, the UK RWE study showed no evidence of long-term survival benefits for patients; by Month 24, just [redacted]% of patients were still alive and [redacted]% of patients were progression free – [redacted] the percentage of patients who were alive and progression-free in GARNET, respectively.

The marked and sustained OS benefit associated with dostarlimab clearly and conclusively highlights how dostarlimab would represent a critical addition to the treatment armamentarium, providing hope to patients with recurrent or advanced dMMR/MSI-H EC that has progressed on

or after platinum-based chemotherapy who currently feel abandoned and who currently face an extremely dire prognosis with almost no chance of receiving effective treatment. The PFS and response rates detailed below only further serve to highlight the clinically significant efficacy that dostarlimab would provide, relative to current clinical management in the UK.

Progression-free survival

In GARNET, [redacted]% and [redacted]% of patients in the ITT population had not experienced disease progression or death at Month 12 and Month 24, respectively. The majority of PFS events occurred in the first six months, and the PFS curve subsequent plateaued when approximately [redacted]% of patients had experienced disease progression of death.

This means that the median PFS of [redacted] months is highly uncertain, and associated with very wide CIs (95% CI: [redacted], [redacted]). This is illustrated in Section B.2.7.1, [redacted] from [redacted] months to [redacted] months. [redacted], which is line with the long-term benefit observed from other I-O treatments, suggesting that patients who remain progression-free initially may experience a long-term PFS benefit from dostarlimab treatment through to Month 18 and Month 24, with [redacted]% and [redacted]% of patients remaining free of disease progression or death, respectively.

In comparison, patients in the UK RWE study treated with current clinical management faced a far worse prognosis. Just [redacted]% of patients were progression-free at Month 12, and this dropped to just [redacted]% of patients at Month 24 – similar to OS, this was [redacted] the percentage of patients who were progression-free at the same timepoint following treatment with dostarlimab.[13] Accordingly, there was very limited evidence of any long-term PFS benefit associated with current clinical management.

Response rates

Dostarlimab demonstrated a clinically meaningful and robust ORR of [redacted]% (n=[redacted]; 95% CI: [redacted], [redacted]), with [redacted] patients ([redacted]%) achieved a CR, and [redacted] patients ([redacted]%) achieving a PR. The [redacted] of patients who experienced a response to treatment with dostarlimab experienced [redacted] reduction in tumour size versus baseline. Notably, these responses were durable – after a median follow-up of [redacted] months, the median DOR [redacted], and patients who experienced a response had a [redacted]% ([redacted]) and [redacted]% ([redacted]) of experiencing an ongoing response at Month 12 and Month 18, respectively.

These response rates to dostarlimab are striking in comparison to current clinical management. ESMO guidelines highlight that for patients with EC recurring after first-line chemotherapy, only paclitaxel has consistently shown a response rate >20%, less than half the ORR achieved by dostarlimab. In recently conducted RCTs, McMeekin *et al.* (2015)[6] reports an ORR of 15.7% for patients receiving either paclitaxel or doxorubicin monotherapy (N=223); no patients experienced a CR. For patients receiving doxorubicin monotherapy (N=225), the ZoptEC study reported an even lower ORR of 14.1%, with only 2.0% of patients experiencing a CR.[8-10]

HRQoL

Treatment with dostarlimab preserved patient-reported HRQoL from baseline, as measured by both the EQ-VAS and EORTC QLQ-C30. The results of the EQ-VAS showed an [redacted], while results of the EORTC QLQ-C30

showed that patient-reported pain, fatigue symptoms and physical functioning showed a [redacted] above baseline starting at Cycle 2, 3 and 4, respectively. For patients that did experience symptomatic AEs, the majority remained that these AEs remained stable of improved of the course of their treatment relative to baseline.

Safety and tolerability

Overall, dostarlimab was shown to be well-tolerated. The majority of treatment-related TEAEs were of low grade; only [redacted]% of patients reported any Grade ≥3 treatment-related TEAE. Discontinuation as a result of treatment-related AEs was low ([redacted]%). The most frequent treatment-related TEAEs were diarrhoea ([redacted]%), asthenia ([redacted]%), fatigue (13.2%) and nausea (12.4%). In total, [redacted] patients experienced a ≥ Grade 3 treatment-related TEAE; the most frequently observed events were anaemia in [redacted] patients ([redacted]%) and lipase increased in [redacted] patients ([redacted]%).

Overall, the safety data suggest that the AE profile of dostarlimab is aligned with other currently licensed anti-PD-L1 I-O therapies, and with no unexpected AE signals identified at the time of IA2 (DCO 1st March 2020).

Patients treated with dostarlimab experience a reduced burden of toxicity when compared with cytotoxic chemotherapy. Overall, [redacted]% of patients receiving dostarlimab in GARNET experienced any treatment-related TEAE; in comparison, 90% of patients receiving paclitaxel or doxorubicin monotherapy in McMeekin *et al.* (2015)[6], and almost all of the patients receiving doxorubicin monotherapy in ZoptEC (96.4%) experienced a treatment-related TEAE.[8-10]

Comparative efficacy

The results of the adjusted comparisons between dostarlimab in GARNET and current clinical management in the UK RWE study supported the findings of the unadjusted comparisons, indicating that patients treated with dostarlimab experience significantly increased OS compared to patients treated with current clinical management. The results of the two scenarios with the largest ESSs produced adjusted OS HRs between dostarlimab and clinical management of [redacted] (95% CI: [redacted], [redacted]) (scenario 1A) and [redacted] (95% CI: [redacted], [redacted]) (scenario 2), respectively, compared to an unadjusted OS HR of [redacted] (95% CI: [redacted], [redacted]).[13] These results suggest that the UK RWE GARNET-like cohort was closely matched to the GARNET ITT population, and any remaining differences between the two populations may mean that the true OS benefit associated with dostarlimab is slightly underestimated within the unadjusted comparisons.

These findings in terms of an OS benefit for dostarlimab versus comparator therapies were supported by ITCs versus two published RCTs, ZoptEC and McMeekin *et al.* (2015), which demonstrated clear evidence that dostarlimab provided a marked OS benefit compared to doxorubicin monotherapy.[6, 8-10] Patients treated with dostarlimab with [redacted]% less likely to die compared to doxorubicin monotherapy in ZoptEC (HR: [redacted]; 95% CI: ([redacted], [redacted]); p[redacted]) and [redacted]% less likely to die at any given timepoint compared to patients receiving paclitaxel or doxorubicin monotherapy in McMeekin *et al.* (2015)[6] (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]).[8-10]

Four additional MAICs were conducted against other published studies, although these MAICs are associated with substantially increased uncertainty relative to the comparisons described above. These MAICs were conducted versus retrospective, single-arm studies, and the lack of intra-trial randomisation means that the MAICs cannot account for any prognostic variable imbalances that were not reported, introducing an unknown level of bias and representing a key

concern, given the paucity of patient characteristics that were reported for these studies. Of the three key prognostic variables identified by clinicians, the number of lines of prior anti-cancer therapy was not reported by any of these four studies, and ECOG PS was only reported by Makker *et al.* (2013).[11] The small sample sizes of these studies (N=17, N=41, N=20 and N=31) creates additional uncertainty. As such, it is difficult to draw any conclusions with any certainty versus the remaining four MAICs.

B.2.11.2 Strengths of the clinical evidence base

GARNET

The clinical evidence presented as part of the submission has been derived from a comprehensive SLR that was conducted according to the principles of systematic reviewing published in the Cochrane Handbook.

GARNET, a single-arm, open label trial was the only clinical trial identified for dostarlimab from the SLR. This trial represents the key evidence for efficacy and safety for dostarlimab, and is the largest dataset evaluating the anti-PD-1 in recurrent or advanced EC to date. GARNET was conducted as a single-arm trial, yet despite the single-arm nature of the trial, the CASP risk for bias tool determined that exposure in the GARNET trial was accurately measured through validated, objective measurements including ORR, DOR, DCR, PFS, which minimised bias.

The results of GARNET are relevant to the decision problem specified in the NICE final scope, which proposes the use of dostarlimab for patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or after platinum-based chemotherapy. The external validity of GARNET is supported by the following:

- **Population**: All of the patients in Cohort A1 of the GARNET trial were confirmed to have received prior platinum-based chemotherapy, and all patients were confirmed to have either dMMR/MSI-H or MMR-unk/MSI-H EC. Of the extremely few patients classed as MMR-unk it is highly likely these patients were also dMMR, and this discrepancy results from the fact they were not tested for dMMR status as part of GARNET. The results of GARNET thus provide supportive evidence for the use of dostarlimab in the patient population specified in the decision problem. Furthermore, patients were enrolled in nine UK trial sites, thus increasing the generalisability to the UK recurrent or advanced EC population.
- **Intervention:** Dostarlimab was evaluated in line with its licensed indication, as a treatment option for patients with recurrent or advanced dMMR/MSI-H endometrial cancer that has progressed on or after platinum-based chemotherapy.
- **Comparators:** As a result of the lack of standard of care and absence of clear treatment guidelines in this indication, the primary comparative efficacy analysis in this submission compares dostarlimab to current clinical management in the UK. This consists of aggregate data for a cohort of GARNET-like patients identified in a UK RWE study receiving a range of the most commonly utilised chemotherapy regimens in UK clinical practice. These include the individual chemotherapy regimens listed in the NICE final scope, as well as a range of other chemotherapy regimens that are used in UK clinical practice.
- Whilst the UK RWE study serves as the primary comparative efficacy evidence in this submission, a series of ITCs were also conducted, where possible, between dostarlimab and the individual chemotherapy comparators listed in the NICE final scope, based on published studies identified in the clinical SLR.

- Therefore, despite a paucity of data in the published literature, this submission presents a range of comparative efficacy evidence versus a range of relevant comparators that would be received by patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy in UK clinical practice, including the relevant individual comparators listed in the NICE final scope
- **Outcomes:** The efficacy and safety profile of dostarlimab was demonstrated in a well-defined, homogenous patient population, considering a wide range of outcomes. This included all of the outcomes outlined in the scope that are relevant to clinicians and to patients (ORR, PFS, OS, adverse events, HRQoL).

Comparative efficacy evidence

The principal limitation of the evidence base supporting this submission is the lack of head-to-head evidence for the comparative efficacy between dostarlimab and the relevant comparators to this submission. There was also a distinct paucity of comparator data identified in the clinical SLR; most studies in the relevant patient population were observational studies, where patient characteristics and KM survival data were poorly reported, limiting the quality, and therefore increasing the uncertainty, of any ITCs.

To mitigate the impact of the paucity of data in the literature for the comparators to this submission, GSK conducted a UK RWE study that included a cohort of GARNET-like patients identified via the NCRAS who received a range of chemotherapy regimens that represent current clinical management for patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy, as detailed in Section B.2.7.1.

The UK RWE study provides robust comparative evidence. The NCRAS database collects quality-assured data with complete coverage of all patients diagnosed with cancer in England, meaning that this cohort of [redacted] GARNET like patients are wholly representative of patients in UK clinical practice. These patients were followed-up between 1st January 2013 and 30th September 2020, representing another key strength, particularly for the evaluation of survival endpoints for these patients.

The large sample size of the UK RWE study is a particular strength; the UK RWE study included almost ten times the number of patients in GARNET and four times the number of patients in the relevant arms of the ZoptEC and McMeekin *et al.* (2015), the largest relevant comparator studies identified in the clinical SLR.[6, 8-10] Most importantly, detailed patient characteristics and prognostic variable data were available for all of these patients, allowing the wider population of patients initially identified to be narrowed down to a smaller population of patients that closely matched those in GARNET.

Furthermore, these GARNET-like patients included in the UK RWE study received a wide range of different treatment options reflecting the different options that might be used in clinical practice. Given the clear lack of standard of care treatments for patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy, a comparison with this cohort of patients, the UK RWE GARNET-like cohort, provides a truer reflection of the outcomes that these patients would experience in UK clinical practice, versus the limited data available in the published literature. Furthermore, four of the top five regimens identified in the RWE study align with the regimens listed in the NICE final scope.

Given the generalisability of this RWE cohort to patients with recurrent or advanced EC who

have progressed on or after platinum-based chemotherapy in UK clinical practice, the UK RWE study provides the primary comparative efficacy analysis in this submission, and based on the strengths of the RWE study, the results of the adjusted comparison between dostarlimab and current clinical management inform the base case economic analysis.

Moreover, a comparison of the survival outcomes reported in the UK RWE study with those reported in the published literature supports the generalisability of the UK RWE study to the patient population in GARNET. The median OS estimate of [redacted] months (95% CI: [redacted], [redacted]), from the UK RWE study is similar to median OS estimates from the two relevant RCTs presented in the literature: ZoptEC (10.8 months [95% CI: 9.8, 12.6]) and McMeekin *et al.* (2015) (12.3 months [95% CI: 10.7, 15.4]).[8-10] [6, 13] Similarly, the PFS estimate of [redacted] months (95% CI: [redacted], [redacted]) in the UK RWE study is higher than median PFS estimates in ZoptEC (4.7 months [95% CI: 4.1, 6.6]) and McMeekin *et al.* (2015) (4.0 months [95% CI: 2.7-4.3]), suggesting that the UK RWE study, and the use of TTNT as a proxy for PFS, may result in an overestimation of PFS relative to the published literature.[6, 8-10]

The comparability of the UK RWE GARNET-like cohort to patients in GARNET was further supported by the results of the adjusted comparison between the two studies, which suggested that the two populations were closely matched with minor differences in the unadjusted and adjusted OS HRs. The comparison suggested that any differences between the two populations may actually result in a slight underestimation of the OS benefit of dostarlimab relative to current clinical management.

The availability of IPD from the ZoptEC study, and the subsequent IPTW ITC that could be conducted between dostarlimab and doxorubicin monotherapy, represents another key strength of the comparative efficacy evidence supporting this submission.[8-10] The IPD meant that it was possible to match the populations of GARNET and ZoptEC with respect to a number of key prognostic variables, unlike almost all of the other published studies identified in the clinical SLR.[8-10] The results of the adjusted analysis showed that dostarlimab resulted in an approximate OS benefit of HR: [redacted]; 95% CI: ([redacted], [redacted]); p[redacted]) versus doxorubicin monotherapy, a comparable magnitude of benefit to those observed in the unadjusted (HR: [redacted]) and adjusted comparisons (HR: [redacted] and [redacted], respectively) between dostarlimab and current clinical management in the UK RWE study. The results of the MAIC versus McMeekin *et al.* (2015), the only other RCT that could be included in the comparative efficacy analyses, and the only other trial providing detailed information on inclusion/exclusion criteria and prognostic variables, found a similarly comparable OS HR of [redacted] 95% CI: [redacted], [redacted]; p<[redacted]) between dostarlimab and doxorubicin or paclitaxel monotherapy.[6]

The clear concordance between the OS benefits observed for dostarlimab versus current clinical management in the UK RWE study, versus doxorubicin monotherapy in the ZoptEC study, and versus doxorubicin or paclitaxel monotherapy in the McMeekin *et al.* (2015) study is a key strength of the comparative efficacy analyses.[6, 8-10] These three sources of evidence represent the three most robust sources of comparative efficacy evidence available for this submission, and the fact that they all provide comparable estimates for the OS benefit of dostarlimab versus current clinical management provides additional certainty to the conclusion that treatment with dostarlimab results in a marked improvement in OS relative to current clinical management.

B.2.11.3 Limitations of the clinical evidence base

As outlined previously, the principal limitation of the clinical evidence base supporting this

submission is the lack of head-to-head evidence for the comparative efficacy between dostarlimab and the relevant comparators to this submission. There was also a distinct paucity of comparator data identified in the clinical SLR; most studies in the relevant patient population were observational studies, and patient characteristics and KM survival data were poorly reported, limiting the quality, and therefore increasing the uncertainty, of any ITCs.

While it is reasonable to state that the UK RWE study somewhat mitigates this limitation and provides robust comparative evidence, it is associated with limitations. While OS data were available, the UK RWE study did not include direct PFS data, because the NCRAS database does not include data collection for progression, remission or recurrence of disease. As such, it was necessary to use proxy measures for PFS and disease recurrence. Whilst this measure has been validated by clinical experts, it is likely that the TTNT estimate used represents a conservative estimate because it is likely that patients would experience a delay between disease progression and the initiation of their next line of treatment, the use of proxy does introduce a level of uncertainty.

The differences between PFS in GARNET and TTNT in the UK RWE study precluded the use of a Cox proportional hazards model to conduct an adjusted ITC for PFS, creating additional uncertainty.

The limited comparative PFS analysis represents an overarching limitation to this submission; while alternative robust comparative efficacy evidence is available for OS, it is extremely limited for PFS. It was not possible to conduct an IPTW ITC for PFS based on the ZoptEC study, due to the differences in tumour assessment timepoints between GARNET and ZoptEC, while McMeekin *et al.* (2015)[6] did not report a PFS KM curve.[8-10]

PFS KM curves were reported by Makker *et al.* (2013), Rubinstein *et al.* (2019) and Mazgani et al. (2008), although all of these are small (N≤31), single-arm retrospective studies which reported extremely limited data on patient characteristics and prognostic variables.[11, 59, 60] As a result, while MAICs were conducted versus these studies, the results are associated with an unknown level of bias and a high degree of uncertainty, due to possible imbalances between GARNET and the comparator studies that could not be matched due to the limited patient characteristics reported.

The results of the unadjusted comparison between PFS in GARNET and TTNT in the UK RWE study, and the results of the adjusted comparison between PFS in GARNET and ZoptEC using the main analysis sets indicate that dostarlimab provides a clear PFS benefit versus current clinical management and doxorubicin monotherapy, respectively.[8-10] However, it is difficult to draw any further conclusions on the PFS benefit of dostarlimab versus current clinical management with any uncertainty, given the substantial limitations associated with the other four MAICs.

The substantial limitations associated with Rubinstein *et al.* (2019) and Mazgani *et al.* (2008) introduce a second limitation, meaning that there is no robust comparative efficacy evidence between dostarlimab and carboplatin plus paclitaxel, except for the UK RWE study.[13, 59, 60] It is reasonable to suggest that this represents a minor limitation, given that carboplatin plus paclitaxel was the most frequently received regimen by patients in the UK RWE study ([redacted]%) and therefore carboplatin plus paclitaxel is strongly represented in the efficacy outcomes for current clinical management in the UK RWE study.[59, 60] Nevertheless, the paucity of data for carboplatin plus paclitaxel in the published literature and the substantial uncertainty associated

with the MAICs versus Rubinstein *et al.* (2019) and Mazgani *et al.* (2008) represent a limitation of the comparative efficacy evidence supporting this submission.[59, 60]

Another minor limitation of the comparative efficacy evidence in this submission is that it was not possible to match the populations of patients in any of the comparative efficacy evidence sources with respect to dMMR/MSI-H status, a key inclusion criterion in the GARNET trial. Nevertheless, the impact of this is likely to be minimal, as there is no evidence that MSI-H or dMMR biomarker status has any prognostic or predictive value efficacy and survival outcomes (including recurrence, relapse-free survival, PFS and OS) among patients with advanced or recurrent EC receiving non-anti-PD-(L)1 therapy.[62]

Finally, the UK RWE study only included treatments captured within the SACT dataset; within this dataset drugs which are delivered 'outside' an oncology environment (e.g. in surgical clinics or in primary care) are often poorly recorded. Patients receiving hormone therapy dispensed in primary care or community pharmacies would therefore have been poorly captured in this analysis, with a previous study estimating more than 80% of endocrine therapies captured in an alternative NHSE dataset (Cancer Waiting Times) had not been captured in SACT.[78] Therefore, the UK RWE study likely underestimates the true usage of hormone therapy in UK clinical practice in patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy.[79] As such, while the UK RWE study provides comparative efficacy versus patients receiving current clinical management consisting of chemotherapy regimens in the UK, it does not provide any comparative evidence between dostarlimab and hormone therapy.

The lack of comparative efficacy evidence versus hormone therapy represents a limitation of the submission because it was also not considered feasible to conduct a comparison between dostarlimab and hormone therapy based on the published literature. No directly relevant studies including hormone therapy were identified in the literature including a patient population closely matched to patients in GARNET. A number of studies in patients outside the post-platinum setting were identified, although clinical expert feedback strongly indicated that the survival outcomes reported in these studies would not be reflective of the survival outcomes that would be associated with hormone therapy in the post-platinum setting. Ultimately, it was therefore not possible to conduct a comparison between dostarlimab and hormone therapy.

B.2.11.4 Conclusion

The marked and sustained OS benefit demonstrated between dostarlimab and current clinical management in the UK RWE study, and supported by the results of an adjusted comparison versus the UK RWE study, an IPTW ITC versus ZoptEC and a MAIC versus McMeekin *et al.* (2015) conclusively highlight that dostarlimab would represent a critical addition to the EC treatment armamentarium.[6, 8-10] Dostarlimab would provide hope to patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or after platinum-based chemotherapy who currently feel abandoned and who currently face an extremely dire prognosis with almost no chance of receiving effective treatment. Similar improvements in PFS and response rates for dostarlimab versus current clinical management further serve to highlight the clinically significant efficacy that dostarlimab would provide, relative to current clinical management in the UK.

B.2.11.5 End-of-life criteria

The evidence that dostarlimab meets the end-of-life criteria, as outlined by NICE, are detailed in Table 43 below. Based on UK RWE survival estimates with current clinical management,

together with naïve comparisons versus survival estimates from the literature identified via a clinical SLR for chemotherapy regimens, it is evident that survival for patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or after platinum-based chemotherapy is less than 24 months with currently available treatments, and that dostarlimab provides an extension to current life expectancy of more than three months.

Table 43: End-of-life criteria

<table>
<tr><th>Criterion</th><th>Data available</th><th>Reference in submission</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>

GARNET-like patients in the UK RWE study (N=[redacted]) had a median OS of 10.3 months (95% CI: [redacted], [redacted]) following treatment with currently clinical management consisting of chemotherapy. Two years after the initiation of treatment, only [redacted]% of patients were still alive.
Of the chemotherapy trials identified in the SLR, almost all of the trials reported median OS estimates of less than two years.
Whilst no data were identified in the literature for carboplatin monotherapy and hormone therapy, feedback from UK clinical experts indicated that survival with these therapies would not be expected to exceed that observed in the UK RWE study. UK clinical experts indicated that the median OS for hormone therapy for patients with recurrent or advanced EC who have progressed on or afte platinum based chemotherapy would be approximately [redacted] months.
Taken together, it is evident that dostarlimab is indicated for patients with a short life expectancy, normally less than 24 months.

Table 44: OS estimates from trials identified in the clinical SLR and included in ITCs
<table>
<tr><th>Study</th><th>Chemotherapy</th><th>Median OS, months (95% CI)</th><th>Patients alive at Month 24 (%)</th></tr>
<tr><td>ZoptEC study[8-10] (N=255)</td><td>Doxorubicin monotherapy</td><td>10.8 (9.8, 12.6)</td><td>23.0</td></tr>
<tr><td>McMeekin et al. (2015)[6] (N=248)</td><td>Paclitaxel or doxorubicin monotherapy</td><td>12.3 (10.7, 15.4)</td><td>29.4</td></tr>
<tr><td>Makker et al. (2013)[11] (N=17)</td><td>Doxorubicin monotherapy</td><td>5.8 (1.0, 15.0)</td><td>12.1</td></tr>
<tr><td>Julius et al. (2013)[a, 7] (N=41)</td><td>PLD</td><td>7.0 (NR)</td><td>12.3</td></tr>
<tr><td>Rubinstein et al. (2019)[59] (N=20)</td><td>Carboplatin plus paclitaxel</td><td>27.0 (6.0, 117.0)</td><td>59.5</td></tr>
<tr><td>Mazgani et al. (2008)[b, 60] (N=19)</td><td>Carboplatin plus paclitaxel</td><td>15.0 (9.13, 30.36)</td><td>35.5</td></tr>
<tr><td>Mazgani et al. (2008)[c, 60]</td><td>Carboplatin plus paclitaxel</td><td>26.0 (9.72, 71.4)</td><td>57.2</td></tr>
</table>
</td><td>Section B.2.4.6, Appendix D.4.6</td></tr>
</table>

	(N=12)	
	Footnotes: [a] Patients receiving 40mg/m^2 PLD, which UK clinical experts indicated would be used for patients with EC (Section B.3.2.3). [b] Patients with an endometrioid histology (results were reported separately by histology); [c] Patients with a serous histology (results were reported separately by histology). **Abbreviations:** CI: confidence interval; ITC: indirect treatment comparison; PLD: pegylated doxorubicin; OS: overall survival: RWE: real-world evidence; SLR: systematic literature review	
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• In GARNET, [redacted]% of patients treated with dostarlimab were alive at Month 24. At the time IA2, the median OS was not yet reached (95% CI: [redacted]); a lower 95% CI of [redacted] months suggests that the median OS in GARNET is at least [redacted] months. • Median OS in patients receiving current clinical management based on the UK RWE study was [redacted] months (95% CI: [redacted], [redacted]). • Based on the base case cost-effectiveness analysis, dostarlimab provides an extension to life of [redacted] undiscounted life years (undiscounted life years are reported here to aid comparison with the published literature). • It is therefore evident that dostarlimab provides an extension to life of at least an additional 3 months compared with current NHS treatment.	Section B.2.6.2 and Section B.2.7.1

Abbreviations: CI: confidence interval; EC: endometrial cancer; NHS: National Health Service; NR: not reached; OS: overall survival; RWE: real-world evidence; SLR: systematic literature review.

B.3 Cost-effectiveness

Summary of cost-effectiveness analysis

- A *de novo* partitioned survival model with three health states (progression-free survival [PFS], post-progression survival [PPS] and death) was developed to evaluate the cost-effectiveness of dostarlimab versus current clinical management in patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or after platinum-based chemotherapy.
- The analysis was consistent with the NICE reference case: a cost-utility analysis with a National Health Service (NHS) and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% and a lifetime time horizon was adopted.
- Clinical outcomes (PFS and OS) for dostarlimab were based on the ITT population of the single-arm GARNET study, at the time of the interim analysis (DCO 1st March 2020).
- Clinical outcomes for current clinical management were based on the UK RWE study (detailed in Section B.2.3 and B.2.4). Where possible, scenario analyses using data identified in the literature were conducted for individual comparisons versus the comparator therapies listed in the NICE final scope.
- Health-state utilities for PFS and PPS states were informed by EQ-5D-5L data collected in the GARNET study, cross-walked to the 3L scale and disutilities sourced from the literature were applied for AEs.
- Costs and healthcare resource use captured in the analysis included drug acquisition and administration costs, follow-up and monitoring costs, AE costs, subsequent therapy and end-of-life care costs. Diagnostic testing costs were included in a scenario analysis.

Summary of cost-effectiveness results

- In the base case economic analysis dostarlimab was associated with an additional [redacted] discounted life years (LYs) and an additional [redacted] discounted quality-adjusted life years (QALYs) versus current clinical management. Including the confidential PAS discount for dostarlimab, the base case incremental cost-effectiveness ratio for dostarlimab versus current clinical management was £50,221 per QALY gained.
- Given that patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy are at an end-of-life stage, the base case results demonstrate that dostarlimab represents a cost-effective use of NHS resources when considering the NICE willingness-to-pay threshold of ~£50,000 per QALY gained. Moreover, in the probabilistic sensitivity analysis (PSA), based on 10,000 iterations, there was a [redacted]% chance of dostarlimab being cost-effective at this threshold.
- In the deterministic sensitivity analysis (DSA), the parameters with the greatest effect on the base case ICER were the patient baseline utility, pre- and post-progression health-state utility values for patients >5 cycles from death and the cost per cycle of dostarlimab.
- Extensive scenario analyses were conducted to explore the impact of key model inputs and assumptions. The ICERs for dostarlimab (with PAS) were below the cost-effectiveness threshold of £50,000 per QALY gained across many of the key scenarios, demonstrating the robustness of the base case cost-effectiveness analysis.
- For patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy, dostarlimab represents a step change in the clinical management of this condition and this analysis demonstrates that dostarlimab is a cost-effective use of NHS resources in these patients.

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify any published cost-effectiveness analyses relevant to treatment options for the management of patients with recurrent or advanced EC. Full details of the methodology and results of this SLR are presented in Appendix G.

As detailed in Appendix G.1.4, three publications were identified as economic evaluations including patients with recurrent or advanced EC. Of these, only two studies were economic evaluations for patients with recurrent or advanced EC who had progressed on or after platinum-based chemotherapy: Barrington et al. (2018)[80] and Barrington et al. (2019).[81] Both of these were publications concerning the same study: a US cost-effectiveness analysis of pembrolizumab versus PLD or bevacizumab with patients with recurrent or advanced EC. However, extremely limited data were reported concerning model structure, data sources or the methods applied (time horizon, cycle length, discount rate, etc). The US setting of the economic evaluation also leads to potential concerns regarding generalisability to the UK setting.

Considering these limitations and the paucity of relevant data identified in the economic SLR, a de novo cost-effectiveness model was conducted for the purposes of this appraisal, as detailed in Section B.3.3.2.

Table 45: Summary list of published cost-effectiveness studies identified in the economic SLR

Study	Country	Summary of model	Patient population (average age in years)	QALYs	Costs	ICER (per QALY gained)
Barrington *et al.* (2018)[80]	USA	Evaluation of pembrolizumab compared to PLD or bevacizumab	Patients with recurrent EC that has failed first-line chemotherapy, stratified by patients with MSI-H and MSI-L	NR	NR	MSI-H patients: Pembrolizumab versus PLD: $147,249 Pembrolizumab dominated bevacizumab.
Barrington *et al.* (2019)[81]	USA	Evaluation of pembrolizumab compared to PLD or bevacizumab	Patients with recurrent EC that has failed first-line chemotherapy, stratified by patients with MSI-H and MSI-L	NR	MSI-H patients: Pembrolizumab: $57.9 million Bevacizumab: $30.5 million PLD: $6.0 million	MSI-H patients: Pembrolizumab versus PLD: $147,249 Pembrolizumab dominated bevacizumab.
Chura *et al.* (2010)[82]	USA	A cost-effectiveness analysis of adjuvant treatment strategies for advanced-stage EC	Patients with advanced EC	NR	NR	Whole abdomen radiation: $19,020 Eight cycles of adrianmycin and cisplatin: $26,031 Six cycles of carboplatin, paclitaxel and adriamycin: $25,004 Six cycles of carboplatin and paclitaxel: $37,930 CHEMORAD (whole-pelvis radiation therapy followed by six cycles of adriamycin and cisplatin: $57,860 SANDWICH (three cycles of paclitaxel and carboplatin followed by whole pelvis radiation therapy followed by three cycles of carboplatin and paclitaxel): $75,808

Abbreviations: EC: endometrial cancer; ICER: incremental cost-effectiveness ratio; MSI-H: microsatellite instability – high; MSI-L: microsatellite instability – low; PLD: pegylated liposomal doxorubicin; NR: not reported; QALYs: quality-adjusted life years; USA: United States of America.

B.3.2 Economic analysis

A *de novo* cost-effectiveness model was constructed for this appraisal, as described in the following sections.

B.3.2.1 Patient population

In line with the final NICE scope for this appraisal, and in line with the population included in the GARNET trial and the licensed indication for dostarlimab in the UK, the cost-effectiveness analysis conducted for this appraisal considered patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy.

B.3.2.2 Model structure

Model structure

A *de novo* health economic model was constructed in Microsoft Excel to evaluate the cost-effectiveness of dostarlimab versus relevant comparators in patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy.

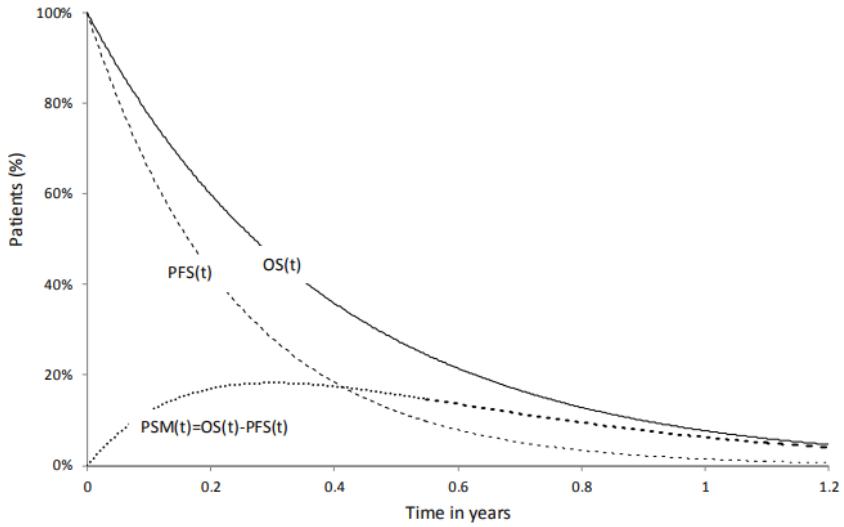
The developed model was a cohort-based partitioned survival model (PSM) consisting of three mutually exclusive health states:

- Progression-free survival (PFS)
- Post-progression survival (PPS)
- Death

The proportion of patients in the PFS state over time was estimated directly from parametric survival curves of PFS, with the proportion of patients in the PPS state estimated as the difference between parametric survival curves for PFS and OS. PFS and OS curves were modelled independently, using different parametric functions, as described in Section B.3.3.4 and Section B.3.3.5. The model structure did not allow for patients to improve their health state, which reflects the progressive nature of EC, and the death health state was an absorbing health state.

Costs, LYs and QALYs were accrued according to the proportion of patients in the PFS and PPS health states over time. An illustrative example of the partitioned survival analysis is presented in Figure 38 below.

Figure 38: PSM structure schematic



Abbreviations: OS: overall survival; PFS: progression-free survival; PSM: partitioned survival model.
Source: NICE Technical Support Document 19.[83]

A PSM structure was deemed appropriate for this decision problem for a number of reasons. Firstly, the PSM model approach is widely used and accepted as appropriate, having been used in several previous NICE single technology appraisals in advanced oncology indications.[83-86]

Secondly, the PSM approach requires substantially fewer inputs than methods that require time- and state-specific transition probabilities to be estimated, such as a Markov model approach.[83] Since the patient distributions between health states are derived directly from trial endpoints (see Section B.3.3.4 and Section B.3.3.5), modelled state populations are well aligned with the GARNET data over the observed trial period, and therefore complexities associated with deriving transition probabilities are avoided.

Finally, the PSM structure provides flexibility in scenario testing, since the parametric and non-standard flexible models applied to the GARNET data can readily be substituted within the model, consistent with the NICE methods guide.[83]

Model characteristics

Clinical outcomes (PFS and OS) for dostarlimab were derived from the GARNET trial, while clinical outcomes for current clinical management were estimated as a basket, based on a UK RWE study conducted by GSK. As discussed in Section B.3.2.3, where possible, scenario analyses using data identified in the literature were conducted for individual comparisons versus the comparator therapies listed in the NICE final scope.

Full details of the clinical efficacy sources used in the model for dostarlimab and relevant comparators are provided in Section B.3.3.2. Full details of the assumptions underlying the cost-effectiveness model are provided in B.3.6.2.

Cost components considered within the economic analysis included treatment acquisition and administration costs, follow-up and monitoring costs, AE costs, subsequent therapy costs, end-of-life costs and diagnostic testing costs. The ICER of dostarlimab versus each comparator was evaluated in terms of the incremental cost per QALY gained.

The analysis was conducted from the perspective of the UK NHS and Personal Social Services in England over a lifetime time horizon. A cycle length of three weeks was adopted in order to sufficiently capture changes in costs and effects over time and to be in line with the frequency of administration of dostarlimab. Both costs and effectiveness estimates were discounted at 3.5% annually in line with the NICE reference case.

A summary of the key features of the *de novo* economic analysis and their justification is provided in Table 46. NICE have not previously conducted any appraisals for patients with EC, so Table 46 summarises this economic analysis for dostarlimab only.

Table 46: Key features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Time horizon	Lifetime horizon (40 years)	The reference case stipulates that the time should be sufficiently long to reflect any differences in costs and outcomes between the technologies being considered.
Clinical parameters	Clinical parameters (PFS and OS) for dostarlimab were derived from the GARNET study. In the base case cost-effectiveness analysis, clinical parameters (PFS and OS) for current clinical management were sourced from the UK RWE study described in Section B.2.3.2. Scenario analyses have been conducted using clinical parameters (PFS and OS) for individual chemotherapy regimens listed in the NICE final scope where data allow. Clinical parameters were identified in the published literature and were then synthesised in multiple indirect treatment comparisons (Section B.2.7.1 and Section B.2.7.2).	GARNET is the most appropriate source of data to estimate the effectiveness of dostarlimab. The UK RWE study provides a comprehensive analysis of treatment patterns and outcomes in the UK and is considered to be the most robust evidence to represent the effectiveness of current clinical management in the UK (Section B.2.3.2). Conversely, there is a paucity of comparator data identified in the literature, including limited patient baseline characteristics and KM curve availability. While multiple ITCs between dostarlimab and the individual chemotherapy regimens listed in the NICE final scope have been conducted where possible, these analyses are associated with a number of limitations. These comparisons are conducted as scenario analyses only, and because of the limitations, the results should be interpreted with caution.
Source of utilities	Health state utility values for the PFS and PPS health states were informed by EQ-5D-5L data collected in the GARNET study, cross-walked to the 3L scale using the Van Hout *et al.* algorithm.[87] The regression model to predict utility values considered baseline utility,	Given the paucity of published utility values for patients with EC, the use of the utility data collected in the GARNET study was considered to represent the most appropriate source. There is a growing body of evidence which highlights that a patient's HRQoL declines substantially in the weeks and months prior to death.[88] As such, time to death was included as a covariate

	progression status and time-to-death as covariates.	alongside baseline utility and progression status in the base case utility analysis.
Source of costs	NHS reference costs PSSRU BNF/eMIT	NHS Reference Costs, PSSRU, BNF and eMIT are standard sources of UK-relevant costs and were used where possible. Where costs were not reported in these sources, cost inputs were sourced from appropriate literature.

Abbreviations: BNF: British National Formulary; EC: endometrial cancer; eMIT: electronic market information tool; ITC: indirect treatment comparison; KM: Kaplan-Meier; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; PSSRU: Personal Social Services Research Unit; RWE: real-world evidence; UK: United Kingdom.

B.3.2.3 Intervention technology and comparators

Intervention: dostarlimab

The dose of dostarlimab incorporated in the economic model was 500 mg every three weeks (Q3W) for the first four cycles (21 days), followed by 1,000 mg every six weeks (Q6W) for all subsequent cycles, in line with the summary of product characteristics (SmPC) for dostarlimab in this indication and the dose received in the GARNET trial.

Comparators

The comparators listed in the NICE final scope include chemotherapy (carboplatin and paclitaxel, paclitaxel monotherapy, doxorubicin monotherapy and carboplatin monotherapy), hormone therapy (such as medroxyprogesterone acetate and megestrol) and best supportive care (BSC). As highlighted in Table 1, BSC is not considered a relevant comparator in this submission and a comparison versus BSC has not been conducted.

As described in Section B.2.1, an SLR was conducted to identify relevant clinical evidence for the efficacy and safety of the relevant comparators in this indication. Only 13 unique studies that investigated relevant chemotherapy regimens in patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy were identified. However, there was a distinct paucity of reported data in the studies identified; most studies in the relevant patient population were observational studies, where patient characteristics and KM survival data were poorly reported, limiting the quality, and therefore increasing the uncertainty, of any potential ITCs. Further, it became clear through discussions with clinicians and via study of the RWE analysis, that for this population, there is no ‘standard of care’; rather a plethora of different treatment options are used, with different practices occurring across the UK.

As a result of the lack of definitive standard of care, and absence of clear treatment guidelines in this indication, the base case cost-effectiveness analysis for this submission compared dostarlimab to current clinical management in the UK using a novel analysis, designed specifically for this NICE submission. It aimed to answer the question: *‘What does current standard of care look like in the UK and what are the outcomes’*? The output consisted of aggregate data for patients receiving a range of the most commonly utilised chemotherapy regimens in UK clinical practice, based on a UK RWE study conducted by GSK using data from the NCRAS (described in Section B.2.3.2).

Base case: current clinical management

As described above, the comparator included in the base case cost-effectiveness analysis was

current clinical management, which comprised the following individual treatment regimens as a basket:

- Carboplatin plus paclitaxel
- Paclitaxel monotherapy
- Carboplatin plus pegylated liposomal doxorubicin (PLD)
- Pegylated liposomal doxorubicin (PLD) monotherapy
- Carboplatin monotherapy
- Hormone therapy (weighted average of medroxyprogesterone and letrozole)

All chemotherapy regimens that were received by ≥5% of patients following platinum-based chemotherapy in the UK RWE study were included as part of current clinical management. Additionally, as hormone therapy was not fully captured in the UK RWE study (detailed in B.2.7.3), an assumption was made to capture it explicitly in the modelling: the basket was re-weighted to include 20% of patients receiving hormone therapy. This resulted in no change to the efficacy associated with current clinical management, but hormone therapy costs and the incidence of AEs (and any associated disutilities) were applied to 20% of the cohort receiving current clinical management, in line with UK clinical expert opinion.[16]

This re-weighting inherently assumes that the effectiveness of hormone therapy is equal to chemotherapy in the UK RWE study, with median PFS and OS estimates of [redacted] months and [redacted] months, respectively. This is likely to be a conservative assumption: UK clinicians confirmed that the median PFS and OS associated with hormone therapy for patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy would be substantially lower than this, at 3 months and 6 months respectively.

The number of patients receiving each treatment in the UK RWE GARNET-like cohort and the re-weighted percentage of patients receiving each treatment, including hormone therapy, as part of current clinical management in the base case cost-effectiveness analysis, are detailed in Table 47. Chemotherapy regimens received by ≥5% of patients in the UK RWE study were included and re-weighted to sum up to 100% (full list of regimens is presented in B.2.3.2, Table 14). In addition, a scenario analysis was conducted using the chemotherapy regimens only (i.e. excluding hormone therapy).

Table 47: Weighting of the individual treatment regimens included as part of current clinical management

Treatment regimen	Patients receiving each treatment in the UK RWE GARNET-like cohort (N=[redacted])	Percentage of patients receiving each treatment regimen as part of current clinical management
Carboplatin plus paclitaxel	[redacted]	[redacted]
Carboplatin plus PLD	[redacted]	[redacted]
PLD monotherapy	[redacted]	[redacted]
Paclitaxel monotherapy	[redacted]	[redacted]
Carboplatin monotherapy	[redacted]	[redacted]
Hormone therapy	[redacted]	[redacted]

Abbreviations: PLD: pegylated liposomal doxorubicin; RWE: real-world evidence.
Source: GSK Data on File[13]

The dosing regimens for each of the treatment regimens included within the current clinical management comparator in the base case cost-effectiveness analysis are presented in Table 48. Almost all of the treatment regimens are not licensed for the treatment of patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy. As such, the dosing regimens have been referenced from the SmPCs in ovarian cancer, or other relevant oncology indications where appropriate, and these dosing regimens were validated by UK clinical experts.[16]

All of the dosing regimens for individual chemotherapy treatments are based on patient body surface area (BSA) or estimated glomerular filtration rate (eGFR). The baseline characteristics of the ITT population from the GARNET trial were used to estimate the total doses required for each patient in the model (Table 49).

Table 48: Dosing regimens for dostarlimab and the treatment regimens included as part of current clinical management in the base case cost-effectiveness analysis

Treatment regimen	Specific treatment	Dosage	Source
Dostarlimab			
Dostarlimab	Dostarlimab cycles 1–4	500 mg Q3W	Draft dostarlimab SmPC,[1] in line with GARNET
	Dostarlimab cycles 5+	1,000 mg Q6W	
Current clinical management for the GARNET-like cohort of patients in the UK RWE study			
Carboplatin plus paclitaxel	Carboplatin	501 mg Q4W (AUC 5)	Carboplatin SmPC[89] Calculated using the Calvert formulae based on estimated eGFR from serum creatinine in GARNET
	Paclitaxel	175 mg/m^2 Q3W	Paclitaxel SmPC[77]
Paclitaxel monotherapy	Paclitaxel	80 mg/m^2 QW	GSK Data on File (clinical expert opinion)[16]
Carboplatin plus PLD	Carboplatin	501 mg Q4W (AUC 5)	Carboplatin SmPC[89] Calculated using the Calvert formulae based on estimated eGFR from serum creatinine in GARNET
	PLD	40 mg/m^2 Q4W[a]	GSK Data on File (clinical expert opinion)[16]
PLD monotherapy	PLD	40 mg/m^2 Q4W[a]	GSK Data on File (clinical expert opinion)[16]
Carboplatin monotherapy	Carboplatin	501 mg Q4W (AUC 5)	Carboplatin SmPC[89] Calculated using the Calvert formulae based on estimated eGFR from serum creatinine in GARNET
Hormone therapy			
Hormone therapy[b]	Medroxyprogesterone acetate	400 mg QD	Medroxyprogesterone acetate SmPC[90]

	Letrozole	2.5 mg QD	Letrozole SmPC[91] (alternative indications)
Individual chemotherapy regimens not listed above considered in scenario analyses			
Doxorubicin monotherapy	Doxorubicin	60 mg/m2 Q3W	Doxorubicin SmPC[76] GSK Data on File (clinical expert opinion)[16]

Footnote: [a] 50 mg/m^2 Q4W PLD is the dosage used in ovarian cancer[92], however, UK clinical expert feedback indicated that a dosage of 40 mg/m^2 would be used for patients with EC. [b] Hormone therapy was included as a weighted average between medroxyprogesterone acetate and letrozole, based on UK clinical expert feedback; of the 20% of patients receiving hormone therapy, half received medroxyprogesterone acetate and half received letrozole.
Abbreviations: AUC: area under the curve; PLD: pegylated liposomal doxorubicin; QD: once daily; QXW: once every X weeks; SmPC: summary of product characteristics.

Scenario analyses: individual chemotherapy comparators and hormone therapy

Given the distinct paucity of data identified in the literature for each of the individual chemotherapy comparators and hormone therapy listed in the NICE final scope, robust comparisons versus these treatments were extremely difficult. Where possible, scenario analyses versus the individual comparator treatments listed within the NICE final scope, including doxorubicin monotherapy, paclitaxel monotherapy and carboplatin plus paclitaxel, have been conducted, using the available data that was sourced from the literature detailed in Section B.2.7.1 and B.2.7.2.

As discussed in Table 5, Section B.2.2 and Section B.2.7.3, no data were identified for either hormone therapy or carboplatin monotherapy within the literature. Despite efforts made to identify alternative sources of data for these comparators, feedback from UK clinical experts strongly indicated that any data for patients not in the post-platinum chemotherapy setting would not be suitable to use as a proxy for these comparators, and that it would not be expected that the efficacy of hormone therapy or carboplatin would exceed that observed in the UK RWE study.[16]

As such, it was not possible to conduct a clinical comparison between dostarlimab and hormone therapy or carboplatin monotherapy in this submission. In order to estimate the cost-effectiveness of dostarlimab versus each of these treatments, scenarios have been conducted assuming that hormone therapy is equal to the efficacy of current clinical management, and that carboplatin monotherapy has equal efficacy to doxorubicin monotherapy (see Section B.3.8.3).

B.3.2.4 Subsequent therapies

It was assumed that patients receiving either dostarlimab or current clinical management could receive subsequent treatments, based on the percentage of patients receiving subsequent treatment in GARNET and 3L treatment in the UK RWE study, respectively.

In the base case cost-effectiveness analysis, [redacted]% of patients in the dostarlimab arm were assumed to receive subsequent treatment. This percentage was calculated based on the total number of patients who received subsequent treatment in GARNET, [redacted] patients ([redacted]%) of the GARNET ITT population (N=129), divided by the total number of patients (N=[redacted]) who had discontinued dostarlimab by the time of the IA2 (DCO 1st March 2020).

$$\frac{\text{Patients receiving subsequent therapy}}{\text{GARNET ITT population} - \text{patients on treatment at the data cutoff}} = \frac{[redacted]}{129 - [redacted]} = [redacted]\%$$

The distribution of subsequent treatments received by patients in the dostarlimab arm were based on the treatments received by ≥5% of patients in the UK RWE GARNET-like cohort (detailed in Section B.2.3.2, Table 14). In addition, hormone therapy and radiotherapy were not captured in the UK RWE study, so based on clinical expert feedback, it was assumed that 5% and 10% of patients receiving subsequent treatment would receive hormone therapy and radiotherapy, respectively.[16]

The percentage of patients assumed to receive subsequent treatment following current clinical management was calculated as the proportion of patients in the UK RWE GARNET-like cohort who received a subsequent chemotherapy treatment (N=[redacted]) out of the total number of patients in the UK RWE GARNET-like cohort (N=[redacted]); [redacted]%, plus the proportion of patients who would receive subsequent treatment with hormone therapy and radiotherapy. The distribution of subsequent treatments received by patients in the current clinical maangement arm were based on the *subsequent* treatments received by ≥5% of patients in the UK RWE GARNET-like cohort. Similarly, as hormone therapy and radiotherapy were not captured in the UK RWE study, it was assumed that an additional 5% and 10% of patients would receive subsequent treatment with hormone therapy and with radiotherapy, respectively, resulting in a total of [redacted]% of patients receiving subsequent treatment following current clinical management.

A scenario analysis was conducted where the distribution of subsequent treatments received by patients in the dostarlimab arm was based on the subsequent treatments received in the GARNET trial. The subsequent treatment distribution from GARNET was not included in the base case cost-effectiveness analysis due to the limited follow-up for patients in GARNET, and small sample size, as not all patients had discontinued treatment with dostarlimab at the time of the interim analysis (DCO 1st March 2020). In addition, patients were included worldwide in the GARNET trial, while the treatments received in the UK RWE study were considered to provide a more robust representation of the subsequent treatments that patients would receive in UK clinical practice following treatment with dostarlimab.

A summary of the subsequent treatment distributions adopted in the base case cost-effectiveness analysis and scenario analysis are presented in Appendix P.1. These were validated by UK clinical experts, who agreed that the rates of subsequent treatments were considered to be aligned with what would be seen in UK clinical practice. The costs associated with patients receiving subsequent treatment are described in Section B.3.5.5.

B.3.3 Clinical parameters and variables

B.3.3.1 Patient characteristics

The patient baseline characteristics for the modelled patient cohort are provided in Table 49. These were based on the baseline characteristics of patients in the ITT population (N=129) in the GARNET study at the time of the interim analysis (DCO: 1st March 2020).

The mean age was used alongside England and Wales life tables (2017-2019) to calculate the natural mortality of the general population (see survival inputs and assumptions in Section B.3.3.6). The average BSA, serum creatinine and weight were used to calculate drug acquisition costs where dosage was based on these parameters.

Table 49: Patient baseline characteristics of the base case economic analysis

Model parameter	Value	Source
Mean age, years (SD)	[redacted]	GARNET ITT Population (Table 15, Section B.2.4.1)
Mean height at baseline, cm (SD)	[redacted]	GARNET ITT Population (Table 15, Section B.2.4.1)
Mean weight at baseline, kg (SD)	[redacted]	GARNET ITT Population (Table 15, Section B.2.4.1)
BSA, m^2 (SD)	[redacted]	Derived using the Dubois formula, using the weight and height reported for the GARNET ITT population (Table 15, Section B.2.4.1)
eGFR, mL/min	[redacted]	Calculated from mean serum creatinine at baseline in the GARNET ITT population (Table 15, Section B.2.4.1)

Abbreviations: BSA: body surface area; eGFR: estimated glomerular filtration rate; ITT: intention-to-treat; SD: standard deviation.

B.3.3.2 Clinical outcomes

The principal clinical outcomes considered within the economic model were PFS and OS.

Dostarlimab

PFS and OS data for dostarlimab were based on the PFS and OS results for the ITT population (N=129) of the GARNET trial at the time of the IA2 DCO (1st March 2020), as described in Section B.2.4.5 and B.2.4.6.

Current clinical management

Given the single-arm nature of the GARNET trial, it was necessary to identify comparator PFS and OS data for current clinical management. The UK RWE study provided the comparative efficacy evidence used to inform the base case cost-effectiveness analysis, based on a large sample size (N=[redacted]), robust data set, and the pertinent English setting of the RWE study (see Section B.2.3.2).

A number of scenario analyses were conducted exploring the use of alternative sources of efficacy data for current clinical management based on the UK RWE study, as well as pairwise comparisons versus individual chemotherapy regimens based on the published literature, and hormone therapy using the UK RWE study as a proxy. These scenarios are detailed in Section B.3.8.3.

B.3.3.3 Survival inputs and assumptions

As described in Section B.3.2.2, the proportion of patients in the PFS, PPS and death health states at each cycle in the model were defined by PFS and OS curves. As the follow-up periods for the relevant studies (GARNET and the UK RWE study) were shorter than the model time horizon (40 years), extrapolations from the observed PFS and OS data were required.

In accordance with the NICE DSU TSD 14 guidance on survival analyses, a range of standard parametric distributions (exponential, Weibull, log-logistic, lognormal, Gompertz and generalised gamma) were explored.[93] The gamma model and flexible models (i.e. spline models) were also

considered for dostarlimab extrapolation. Spline models were developed based on the algorithm by Royston and Parmar *et al.* (2002).[94] One- and two- knot cubic spline models were considered using the Flexsurvspline function in R. The goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criterion [BIC]) were then estimated for each parametric function.

In determining the choice of survival model for the base case for dostarlimab and for current clinical management, consideration was given to the following, according to the recommendations provided in NICE DSU TSD 14[93]:

- Assessment of the proportional hazards assumption between dostarlimab in GARNET and current clinical management in the UK RWE GARNET-like cohort, in order to assess whether joint or separate statistical models were more appropriate for the two treatments, with respect to each endpoint
- AIC and BIC goodness-of-fit statistics (i.e. statistical fit) were calculated in order to assess how well the statistical models fitted to the observed data
- Visual inspection of the extrapolated curves versus the observed Kaplan-Meier curves
- Clinical plausibility for both short-term and long-term estimates of survival based on discussion with UK clinical experts

Based on NICE DSU TSD 14 guidance, the proportional hazards assumption was tested for each clinical endpoint.[93] This was primarily assessed using the log-cumulative hazard plots (i.e. if the plots overlapped) and Schoenfeld residual test (i.e. if the p-value ≤ 0.05) to confirm the validity of proportional hazards. When the proportional hazards assumption did not hold, parametric models were fitted separately to each treatment arm.

Additionally, in order to ensure that any OS extrapolations did not provide implausible estimates of mortality, all mortality rates used in the model were bound by the age- and gender-specific natural mortality of the general population as a minimum (calculated using England and Wales life tables [2017–2019]). Adjustments were made in the model traces to ensure that logical inconsistencies, such as the proportion of patients alive being less than the proportion of patients alive and progression-free, could not occur (i.e. PFS was bound by OS as a minimum).

B.3.3.4 Treatment waning

As detailed later in Section B.3.3.7, the base case cost-effectiveness analysis assumed that [redacted]% of patients receiving dostarlimab continue to receive treatment beyond [redacted], with [redacted] assumed to discontinue treatment after [redacted]. In order to account for the impact of this on the long-term efficacy associated with dostarlimab specifically within the current base case extrapolations (particularly the generalised gamma curve for OS, which has a 'fat' tail) treatment waning assumptions were applied in line with UK clinical expert feedback and previous appraisals of I-O therapies.[85, 86, 95, 96]

In the base case cost-effectiveness analysis, treatment waning was applied to the dostarlimab PFS and OS extrapolations and was assumed to start at [redacted] months, [redacted] months following the timepoint by which [redacted] of patients have discontinued treatment with dostarlimab. Treatment waning was assumed to end at [redacted], at which point, the efficacy associated with dostarlimab was assumed to be equal to the efficacy associated with current clinical management. These assumptions were based on feedback from UK clinical experts.

B.3.3.5 Progression-free survival

Assessment of proportional hazards

A visual comparison of the KM curve for PFS in GARNET and TTNT in the UK RWE cohort suggests non-proportionality of hazards. Log-cumulative hazard plots show that the two curves cross twice, once between log ([redacted]) months, and a second time at approximately log ([redacted]) months (Figure 39) and Schoenfeld residual tests reported a p<[redacted] (Figure 40), confirming that the proportional hazards assumption was violated between PFS in GARNET and TTNT in the UK RWE cohort.

Based on these results, it was necessary to fit separate parametric models to PFS in GARNET, and TTNT in the UK RWE GARNET-like cohort. The choice of parametric models is described in the following sections.

Figure 39: Log cumulative hazard plot between PFS in GARNET and TTNT in the UK RWE study

Abbreviations: PFS: progression-free survival; TTNT: time-to-next-treatment; RWE: real-world evidence; UK: United Kingdom.

Figure 40: Schoenfeld residual plot between PFS in GARNET and TTNT in the UK RWE study

Abbreviations: PFS: progression-free survival; TTNT: time-to-next-treatment; RWE: real-world evidence; UK: United Kingdom.

Dostarlimab

The standard parametric distributions described in Section B.3.3.3 were fitted to the BICR PFS IPD for the ITT population (N=129) from GARNET. The AIC and BIC values for each of the extrapolations are summarised in Table 50. Extrapolations of PFS using each model up to five years are presented in Figure 41 for all functions, to aid investigation of the visual fit of the distributions to the observed study data, and extrapolations using each model up to 40 years are presented in Figure 42 to aid investigation of the clinical plausibility of long-term extrapolations. The extrapolations presented below include a treatment waning effect, as detailed previously in Section B.3.3.4.

The clinical plausibility of the long-term extrapolations was assessed using feedback from UK clinical experts, who were asked to estimate the percentage of patients who would be progression-free following treatment with dostarlimab at various time intervals (3, 5, 10, 15 and 20 years). These estimates are presented in Table 51.

The first radiological tumour response assessment in GARNET resulted in a protocol-driven drop in PFS by BICR at Week 12, which impacted the ability of standard parametric models to adequately fit to PFS data. Therefore, flexible spline models (one- and two- knots) were also explored (Appendix P.3). Spline curves performed well in terms of statistical fit measured by AIC/BIC (Table 50). However, it was clear that they overestimated long-term PFS and were considered clinically implausible (based on the clinical expert estimates detailed in Table 51) compared to the standard parametric models. As such, they were not considered any further.

An alternative approach was also explored, whereby the KM data from GARNET were applied directly for an initial period of time, after which point, a standard parametric distribution would be fitted to the remainder of the KM curve. This approach partially mitigated the poor fit of the

standard parametric distributions to the initial part of the KM curve. However, once the PFS KM curve begins to flatten, the hazard approaches zero, and there was insufficient follow-up to model a parametric distribution starting from a later timepoint (if the KM data is applied directly initially). As such, this approach was not considered further.

Table 50: Summary of goodness-of-fit data for dostarlimab PFS (GARNET ITT population); standard parametric and spline models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard with single knot	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard with two knots	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; PFS: progression-free survival.

Figure 41: Dostarlimab PFS extrapolations up to five years (GARNET ITT population) (treatment waning applied)

Abbreviations: PFS: progression-free survival.

Figure 42: Dostarlimab PFS extrapolations up to 40 years (GARNET ITT population) (treatment waning applied)

Abbreviations: PFS: progression-free survival.

Table 51: Summary of clinical expert estimates[a] for the percentage of patients who would be progression-free at various time intervals following treatment with dostarlimab

	Percentage of patients who would be progression-free at each time interval, %							
Time	Response 1	Response 2	Response 3	Response 4	Response 5	Response 6	Response 7	Mean
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: [a] Responses were provided anonymously, and it is not possible to identify all of the responses from any one respondent. The responses presented above are arbitrarily ordered from low to high, and therefore all of the responses in each column were not necessarily provided by the same respondent.
Source: GSK Data on File.[16]

Based on the statistical fit rankings in Table 50, coupled with the UK clinical expert opinion on the extrapolations (akin to those presented in Figure 41 and Figure 42) and their estimates of the percentage of patients who would be progression-free at future timepoints (Table 51), the generalised gamma and Gompertz models provided were identified as having the best fit to the observed KM data. However, based on plausibility considering the OS extrapolations, a more conservative survival curve, the lognormal, was identified for use in the base case:

- The generalised gamma model represented the most plausible extrapolation, predicting that [redacted]%, [redacted]%, [redacted]% and [redacted]% of patients would be progression-free at 5, 10, 15 and 20 years, respectively, which aligned with the clinical expert estimates in Table 51, slightly underestimating PFS at 5 and 10 years. However, when the generalised gamma model was considered alongside the clinical expert estimate for the percentage of patients alive at 5, 10, 15 and 20 years, respectively (presented in Section B.3.3.6, Table 58), then it also appeared

clinically implausible. The mean clinical expert estimates for the percentage of patients **alive** at 5, 10, 15 and 20 years were [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively. These estimates were closely aligned with the mean clinical expert estimates for the percentage of patients who would be **progression-free** (Table 51), particularly at 10 years ([redacted]% alive versus [redacted]% progression-free), 15 years ([redacted]% alive versus [redacted]% progression-free) and 20 years ([redacted]% alive versus [redacted]%). Such a close alignment between PFS and OS was considered to be clinically implausible, and as such, the generalised gamma extrapolation was excluded in order to prioritise choosing a clinically plausible PFS extrapolation in line with the clinical expert OS estimates, rather than the clinical expert PFS estimates.

- Alongside the generalised gamma model, the spline models (one and two knots) and the Gompertz model provided the best statistical fit to the observed data. However, these models were not considered to provide a clinically plausible long-term extrapolation, estimating that [redacted]% (Gompertz), [redacted]% (spline hazard with one-knot) and [redacted]% (spline hazard with two-knot) of patients would be alive after 40 years, while the mean of the clinical expert responses indicated that only [redacted]% of patients would be progression-free at 20 years (Table 51)
- Once the Gompertz and generalised gamma models and the two spline models were excluded for clinical implausibility, the lognormal and log-logistic models provided the next best statistical fit to the observed KM data, with the 5th and 6th lowest AIC and BIC rankings, respectively. Both models were more conservative than the clinical expert estimates, with the lognormal model predicting that [redacted]%, [redacted]%, [redacted]% and [redacted]% of patients would be progression-free after 5, 10, 15 and 20 years, respectively. However, the lognormal model represented the best fitting, clinically plausible model, once the Gompertz, generalised gamma and spline models were excluded for clinical implausibility. As such, the lognormal model was chosen in the base case cost-effectiveness analysis. The log-logistic and generalised gamma models were considered in scenario analyses.

Current clinical management

As described in Section B.2.3.2 and B.2.11.3, because the NCRAS database does not include data on progression, remission or recurrence of disease, the UK RWE study could not capture PFS data. It was therefore necessary to use TTNT as a proxy measure for PFS. Whilst this measure was validated by clinical experts, UK clinical experts confirmed that TTNT represents a conservative estimate and likely overestimates PFS, because it is likely that patients would experience a delay between disease progression and the initiation of their next line of treatment. Nevertheless, UK clinical experts agreed that TTNT represented the best available proxy for PFS from the RWE study and this was subsequently used in the base case economic analysis.

IPD were not available as part of the UK RWE study. As such, the KM curves for TTNT for the GARNET-like cohort of the UK RWE study were used to approximate pseudo-IPD using the methods detailed in NICE DSU TSD 14.[93] The KM curves were digitised to provide a series of coordinates corresponding to survival rates over time and an adaptation of the algorithm developed by Guyot *et al.* (2012) was performed in R to map from these coordinates, alongside corresponding risk tables, to approximate the IPD.[73]

The standard parametric distributions described in Section B.3.3.3 were fitted to the TTNT pseudo-IPD for the GARNET-like cohort of the UK RWE study (N=[redacted]). The AIC and BIC values for each of the extrapolations are summarised in Table 52.

Extrapolations of PFS using each model up to five years and 40 years are presented in Figure 43 and Figure 44, respectively, and represent current clinical management. The clinical plausibility of the long-term extrapolations was assessed using feedback from UK clinical experts, who were asked to estimate the percentage of patients who would be progression-free following treatment with current clinical management at 5, 10, 15 and 20 years. The responses are presented in Table 53.

Table 52: Summary of goodness-of-fit data for PFS (based on TTNT) for current clinical management (GARNET-like cohort in the UK RWE study) – standard parametric and flexible models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Standard parametric models				
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; RWE: real-world evidence; TTNT: time to next treatment; UK: United Kingdom.

Figure 43: UK RWE GARNET-like cohort PFS extrapolations (based on TTNT) up to five years

Abbreviations: PFS: progression-free survival; RWE: real-world evidence; TTNT: time to next treatment; UK: United Kingdom.

Figure 44: UK RWE GARNET-like cohort PFS extrapolations (based on TTNT) up to 40 years

Abbreviations: RWE: real-world evidence; TTNT: time to next treatment; UK: United Kingdom.

Table 53: Summary of clinical expert estimates for the percentage of patients who would be progression-free at various time intervals following treatment with current clinical management

	Percentage of patients who would be progression-free at each time interval, %							
Timepoint	Response 1	Response 2	Response 3	Response 4	Response 5	Response 6	Response 7	Mean
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: Responses were provided anonymously, and it is not possible to identify all of the responses from any one respondent. The responses presented above are arbitrarily ordered from low to high, and therefore all of the responses in each column were not necessarily provided by the same respondent.
Source: GSK Data on File.

According to both goodness of fit statistics and visual inspection, the extrapolations for PFS (based on TTNT) were less sensitive to the choice of parametric distribution compared to the PFS extrapolations for dostarlimab, likely due to the increased sample size and longer duration of follow-up in the UK RWE GARNET-like cohort compared to GARNET.

The log-logistic and lognormal curves provided the best statistical fit according to AIC and BIC, respectively. The log-logistic model resulted in clinically plausible long-term extrapolations, predicting that [redacted]%, [redacted]%, [redacted]% and [redacted]% of patients would be progression-free at 5, 10, 15 and 20 years, respectively. These estimates were similar to the clinical expert mean estimates of [redacted]%, [redacted]%, [redacted]% and [redacted]% at the same time points, respectively, slightly underestimating PFS at each timepoint. However, the other parametric models all resulted in slightly lower, albeit similar, estimates of the percentages who were progression-free at each time point, while they also provided a worse statistical fit. As such, the log-logistic model was used in the base case cost-effectiveness analysis, while the lognormal model was considered in a scenario analysis.

In addition to the scenario analyses exploring alternative PFS extrapolations for current clinical management based on the UK RWE study data, a scenario analysis was also conducted using TTD as a potential proxy for PFS, instead of TTNT, as it is likely that the true PFS for current clinical management lies between TTNT and TTD (see Section B.3.8.3).

Summary of base case extrapolations (PFS)

A summary of the base case extrapolations for PFS for dostarlimab and current clinical management is presented in Table 54. Additionally, scenario analyses were conducted varying the extrapolations for dostarlimab or current clinical management (Section B.3.8.3).

Table 54: Summary of the base case extrapolations for PFS for dostarlimab and current clinical management

	Dostarlimab	Current clinical management
Base case extrapolation	Lognormal	Log-logistic

Abbreviations: PFS: progression-free survival.

B.3.3.6 Overall survival

Assessment of proportional hazards

The results of the proportional hazards assessment for OS suggested that it was reasonable to assume proportional hazards between patients in GARNET and the UK RWE GARNET-like cohort with respect to OS. The log cumulative hazard plots (Figure 45) appeared to run reasonably parallel, although the two curves did cross once at approximately log [redacted] month. However, the Schoenfeld residual test (Figure 46) suggested that the proportional hazards assumption did hold between the two populations (p=[redacted]).

Figure 45: Log cumulative hazard plot between OS in GARNET and the UK RWE study

Abbreviations: OS: overall survival; RWE: real-world evidence; UK: United Kingdom.

Figure 46: Schoenfeld residual plot between OS in GARNET and the UK RWE study

Abbreviations: OS: overall survival; RWE: real-world evidence; UK: United Kingdom.

Nevertheless, the fitting of independent parametric models was considered to be a more robust approach for the base case cost-effectiveness analysis, given the fundamental difference in mechanism of action between dostarlimab, and the cytotoxic chemotherapies that constitute current clinical management. As described in Section B.1.3.6 and Section B.2.10, dostarlimab is a novel I-O therapy, which enables a patient's own immune system to mount an anti-tumour response. Notably, successful treatment response following I-O therapies manifests differently, and may include a delayed response, compared to conventional cytotoxic chemotherapy, and longer-term treatment benefits even after treatment discontinuation.[52, 65, 66]

Moreover, the application of a HR to the dostarlimab PFS and OS extrapolations, and the joint fitting of the curves, would inherently assume that the comparator chemotherapy will be associated with survival functions that display a similar shape and follow a similar trajectory to the dostarlimab survival functions, including the potential for long-term benefit and the extended tail of the KM curves that is the hallmark of I-O therapies. Based on the published evidence of chemotherapy for patients with recurrent or advanced EC in the post-platinum setting (Appendix D.4.6), this assumption was considered unlikely.

Considering this, and the availability of robust data for current clinical management from the UK RWE GARNET-like cohort (which included [redacted] patients who were followed-up between 1st January 2013 and 30th September 2020), the decision was made to independently fit parametric models to GARNET and the UK RWE GARNET-like cohort in the base case cost-effectiveness analysis.

As the proportional hazards assumption was seen to hold for OS between GARNET and the UK-RWE GARNET-like cohort, a scenario was explored whereby the same extrapolation (generalised gamma) was used for OS for both dostarlimab and current clinical management

(Section B.3.8.3). Additionally, scenario analyses were conducted to explore the use of the OS HRs derived for the UK RWE MAIC (detailed in Section B.2.7.1) to the dostarlimab OS extrapolation (Section B.3.8.3), to explore the impact of any potential differences between the GARNET ITT population and the UK RWE GARNET-like cohort.

Dostarlimab

As with PFS, the standard parametric distributions and flexible models in Section B.3.3.3 were fitted to the OS IPD for the ITT population (N=129) in GARNET. The AIC and BIC values for each of the extrapolations are summarised in Table 55. Extrapolations using each model up to five years and 40 years are presented in Figure 47 and Figure 48, respectively. The extrapolations presented below include a treatment waning effect, as detailed previously in Section B.3.3.4.

In order to review the clinical plausibility of the extrapolations presented, the predicted number of patients alive based on parametric extrapolations were reviewed against feedback from UK clinical experts, who provided estimates for the percentage of patients who would be alive following treatment with dostarlimab at various time intervals (3, 5, 10, 15 and 20 years). The responses are presented in Table 56.

Table 55: Summary of goodness-of-fit data for dostarlimab OS (GARNET ITT population) standard parametric and spline models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard with single knot	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard with two knots	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; OS: overall survival.

Figure 47: Dostarlimab OS extrapolations up to five years (GARNET ITT population) (treatment waning applied)

Abbreviations: OS: overall survival.

Figure 48: Dostarlimab OS extrapolations up to 40 years (GARNET ITT population) (treatment waning applied)

Abbreviations: OS: overall survival.

Table 56: Summary of clinical expert estimates[a] for the percentage of patients who would be alive at various time intervals following treatment with dostarlimab

	Percentage of patients who would be alive at each time interval, %							
Time	Response 1	Response 2	Response 3	Response 4	Response 5	Response 6	Response 7	Mean[b]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Responses were provided anonymously, and it is not possible to identify all of the responses from any one respondent. The responses presented above are arbitrarily ordered from low to high, and therefore all of the responses in each column were not necessarily provided by the same respondent.
[b] Responses predicting less than X patients alive at a given time interval were included as an estimate of X patients in the mean calculations.

The OS extrapolations appeared to provide a good fit to the observed KM data. The generalised gamma and lognormal models provided the best statistical fit according to AIC and BIC, respectively.

These two models were then reviewed against the UK clinical expert estimates for the percentage of patients alive at long-term time points, as detailed in Table 56. The mean clinical expert estimates for the percentage of patients alive at 5, 10, 15 and 20 years were [redacted]%, [redacted]%, [redacted]% and [redacted]%, respectively. With treatment waning applied, the generalised gamma model predicted that [redacted]%, [redacted]%, [redacted]% and [redacted]% of patients would be alive at the same time points, while the lognormal model predicted that [redacted]%, [redacted]%, [redacted]% and [redacted]% of patients would be alive at 5, 10, 15 and 20 years, respectively.

Of the two models, the generalised gamma model was considered to provide the most clinically plausible long-term extrapolations, with predicted landmark survival estimates more closely aligned with the clinical expert feedback. The lognormal model underestimated the patients who would be alive at each timepoint and was considered less clinically plausible.

In addition to the clinical expert feedback, the percentage of patients alive after 5, 10, 15 and 20 years following treatment with dostarlimab is supported by evidence of a number of patients who experience durable responses following treatment with dostarlimab; of the patients who experience a response to treatment with dostarlimab, there was an [redacted]% chance of maintaining the response to Month 18, respectively. This is supported by the outcomes observed for previous I-O therapies, where patients have shown evidence of long-term remission and survival, even following discontinuation of treatment. [52, 65, 66]

As such, the generalised gamma model, inclusive of treatment waning, was chosen as the base case extrapolation for OS, as the model in closest alignment with the clinician predicted estimates of long-term survival. A scenario analysis excluding treatment waning was also considered.

The lognormal model was additionally considered in a scenario analysis, as one of the two models with the best statistical fit, and the next-most clinically plausible long-term extrapolations after the generalised gamma model. However, it is clear that when treatment waning was applied, the lognormal curve substantially underestimated the predicted numbers of patients alive at 5, 10, 15 and 20 years, compared to the clinical expert estimates in Table 56 and is therefore not clinically plausible. As such, the lognormal scenario did not apply a treatment waning effect; the resulting predictions of [redacted]%, [redacted]%, [redacted]% and [redacted]% of patients alive at 5, 10, 15 and 20 years were much more aligned with the clinical expert estimates at each timepoint respectively, and could be considered more clinically plausible, compared to the predictions from the lognormal model with treatment waning applied.

Current clinical management

The KM curves for OS for the GARNET-like cohort of the UK RWE study were used to approximate pseudo-IPD using the methods detailed in NICE DSU TSD 14, and described in Section B.3.3.5 for PFS.[93]

The standard parametric distributions described in Section B.3.3.3 were fitted to the OS pseudo-IPD for the GARNET-like cohort of the UK RWE study (N=[redacted]). The AIC and BIC values for each of the extrapolations are summarised in Table 57.

Extrapolations of OS using each model up to five years and 40 years are presented in Figure 49 and Figure 50, respectively. The clinical plausibility of the long-term extrapolations was assessed using feedback from UK clinical experts, who were asked to estimate the percentage of patients who would be progression-free following treatment with current clinical management at 5, 10, 15 and 20 years. The responses are presented in Table 58.

Table 57: Summary of goodness-of-fit data for OS for current clinical management (GARNET-like cohort in the UK RWE study) – standard parametric and flexible models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Standard parametric models				
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival; RWE: real-world evidence; UK: United Kingdom.

Figure 49: UK RWE GARNET-like cohort OS extrapolations up to five years

Abbreviations: OS: overall survival; RWE: real-world evidence; UK: United Kingdom.

Figure 50: UK RWE GARNET-like cohort OS extrapolations up to 40 years

Abbreviations: OS: overall survival; RWE: real-world evidence; UK: United Kingdom.

Table 58: Summary of clinical expert estimates[a] for the percentage of patients who would be alive following treatment with current clinical management

	Percentage of patients who would be alive at each time interval							
Time	Response 1	Response 2	Response 3	Response 4	Response 5	Response 6	Response 7	Mean[b]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: [a] Responses were provided anonymously, and it is not possible to identify all of the responses from any one respondent. The responses presented above are arbitrarily ordered from low to high, and therefore all of the responses in each column were not necessarily provided by the same respondent. [b] Responses predicting less than X patients alive at a given time interval were included as an estimate of X patients in the mean calculations.
Source: GSK Data on File.

As for PFS, according to both goodness of fit statistics and visual inspection, the extrapolations for OS for the UK RWE were less sensitive to the choice of parametric distribution in comparison to the extrapolations for dostarlimab in GARNET. The log-logistic and lognormal curve provided the best statistical fit according to AIC and BIC. All of the extrapolations resulted in broadly similar landmark survival estimates.

The log-logistic extrapolation predicted that [redacted]%, [redacted]%, [redacted]% and [redacted]% of patients would be alive at 5, 10, 15 and 20 years, respectively, while the lognormal extrapolation predicted that [redacted]%, [redacted]%, [redacted]% and [redacted]% of patients would be alive at 5, 10, 15 and 20 years, respectively. In comparison, the mean clinical expert estimates predicted that [redacted]%, [redacted]%, [redacted]% and [redacted]% of patients would be alive at 5, 10, 15 and 20 years, respectively. While both models slightly underestimated OS compared to the clinical expert estimates, particularly at 5 and 10 years, both models could be considered clinically plausible. Nevertheless, the log-logistic model resulted in the highest landmark survival estimates for all time points after ten years, so was considered to

be more clinically plausible than any of the other models.

As such, and considering the log-logistic model provided the best fit to the observed data, the log-logistic extrapolation was used in the base case cost-effectiveness analysis. A scenario analysis was conducted using the lognormal model.

Summary of base case extrapolations (OS)

A summary of the base case extrapolations for OS for dostarlimab and current clinical management is provided in Table 59. Additionally, scenario analyses were conducted varying the extrapolations for dostarlimab or current clinical management, and two scenarios were conducted where OS for current clinical management was calculated by applying the HRs from Scenario 1 and Scenario 2 of the UK RWE MAIC (detailed in Section B.2.7.1) to the OS extrapolation for dostarlimab (Section B.3.8.3).

Table 59: A summary of the base case extrapolations for OS for dostarlimab and current clinical management

	Dostarlimab	Current clinical management
Base case extrapolation	Generalised gamma	Log-logistic

Abbreviations: HR: hazard ratio; OS: overall survival.

B.3.3.7 Time on treatment

Assessment of proportional hazards

The proportional hazards assessment was violated between ToT in GARNET and TTD in the UK RWE cohort. The log cumulative hazard plots (Figure 51) were shown to cross and not parallel, and the Schoenfeld residual test (Figure 52) confirmed that the proportional hazards assessment was violated (p<[redacted]). As such, it was necessary to fit separate parametric models to ToT in GARNET and TTD in the UK RWE GARNET-like cohort. This process is described in the following sections.

Figure 51: Log cumulative hazard plot between ToT in GARNET and TTD in the UK RWE study

Abbreviations: RWE: real-world evidence; ToT: time on treatment; TTD: time to discontinuation; UK: United Kingdom.

Figure 52: Schoenfeld residual plot between ToT in GARNET and TTD in the UK RWE study

Abbreviations: RWE: real-world evidence; ToT: time on treatment; TTD: time to discontinuation; UK: United Kingdom.

Dostarlimab

In line with the approach for PFS and OS, the standard parametric distributions described in Section B.3.3.3 were fitted to the ToT data for the ITT population (N=129) in GARNET to estimate ToT for dostarlimab within the model. The AIC and BIC values for each of the

extrapolations are summarised in Table 60. Extrapolations of ToT using each model up to five years are presented in Figure 53 for all functions.

UK clinical expert opinion indicates that, regardless of whether patients are continuing to derive clinical benefit from dostarlimab, they would likely not receive dostarlimab any longer than [redacted]: [redacted] still receiving dostarlimab at [redacted] were assumed to discontinue treatment at this point in the base case cost-effectiveness analysis. Long-term extrapolations beyond [redacted] for ToT for dostarlimab were therefore not required.

Table 60: Summary of goodness-of-fit data for dostarlimab ToT (GARNET ITT population) standard parametric and spline models

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Standard parametric models				
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard with single knot	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard with two knots	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; ToT: time on treatment.

Figure 53: Dostarlimab ToT extrapolations up to five years (GARNET ITT population)

[redacted]

Abbreviations: ToT: time on treatment.

The Gompertz and loglogistic models were considered to provide the best statistical fit to the ToT data according to AIC and BIC, respectively.

Currently, the observed data from GARNET estimate that the probability of remaining on dostarlimab at two years is [redacted]%. This is likely an overestimation, considering the KM curve for ToT in GARNET has only [redacted] patients at risk (<[redacted]) beyond 21 months. Censoring towards the

end of the tail (i.e. patients who had a shorter follow-up of less than 24 months were censored even though they may have still been receiving dostarlimab), together with the remaining long time responders in GARNET, led to the plateau observed in the KM data from Month 21 onwards and may reflect an overestimation of the probability of patients remaining on treatment at Month 24 and beyond.

Accordingly, UK clinical experts indicated that based on their clinical experience with other I-O therapies, they would expect the real-world percentage of patients receiving dostarlimab after [redacted] would likely be between [redacted]% and [redacted]%, notably lower than the [redacted]% predicted by the GARNET ToT KM curve, and the percentages of patients on treatment at two years predicted by all of the long-term extrapolations presented in Figure 53.

All of the models, with the exception of the exponential model, could be considered clinically implausible, when reviewed against the clinical expert feedback, with all of the models predicting >[redacted]% of patients receiving treatment at two years. While the exponential model could be considered to be clinically plausible, the exponential model provided the worst statistical fit to the observed data over the first two years and was therefore excluded.

Of the remaining models, the models providing the best statistical fit, the Gompertz model and the spline model with two knots, were considered to be the most clinically implausible, predicting the highest number of patients remaining on treatment at five years ([redacted]% and [redacted]%) of all the models. As UK clinical experts indicated that no more than [redacted]% of patients would continue to receive dostarlimab after [redacted], these models were excluded due to clinical implausibility. Following their exclusion, the log-logistic model provided the next best statistical fit, while also providing slightly more plausible long-term extrapolations for ToT ([redacted]% of patients receiving treatment at five years).

However, while the log-logistic model provides the best statistical fit to the observed data once the Gompertz and spline with two knots were excluded, it still resulted in clinically implausible extrapolations after [redacted]. In order to account for this discrepancy, an adjustment was applied to better reflect the anticipated real-world prescribing of dostarlimab. UK clinical experts indicated that they would expect at least [redacted]% of patients to remain on treatment with dostarlimab following [redacted] and indicated that no more than [redacted]% of patients would continue on treatment.

Time on treatment: adjustment to anticipated real-world prescribing

An adjustment was applied in the base case cost-effectiveness analysis in order to reflect the anticipated real-world prescribing of dostarlimab, which UK clinical experts noted would likely be between [redacted]% and [redacted]%. Considering the uncertainty associated with the true value, the base case cost-effectiveness analysis assumed that [redacted]% of patients would continue to receive dostarlimab after [redacted], while [redacted]% was explored in a scenario analysis.

UK clinical expert opinion indicated that, regardless of whether patients are continuing to derive clinical benefit from dostarlimab, they would likely not receive dostarlimab any longer than [redacted]. As such, [redacted] patients still receiving dostarlimab at [redacted] were assumed to discontinue treatment at this point in the base case cost-effectiveness analysis.

The resulting dostarlimab ToT extrapolation, following adjustment for anticipated real-world prescribing of dostarlimab at [redacted] and [redacted] is presented in Figure 54. The log-logistic extrapolation was followed for the first [redacted], at which point, the patients on treatment were adjusted to account for anticipated real-world prescribing, with [redacted]% of patients continuing

treatment. After [redacted], [redacted] are assumed to discontinue treatment.

Figure 54: Dostarlimab ToT extrapolation adjusted for anticipated real-world prescribing of dostarlimab

Abbreviations: ToT: time on treatment.

A similar dichotomous treatment duration was considered appropriate for decision making in TA517, where clinical expert feedback indicated that the majority of patients receiving treatment with avelumab (an I-O therapy), [redacted], and patients remaining on treatment at five years would immediately discontinue.[97]

In order to investigate the assumptions regarding time on treatment for dostarlimab in the base case cost-effectiveness analysis, scenario analyses were conducted, varying the percentage of patients who are assumed to continue treatment with dostarlimab after [redacted], and the timepoint at which [redacted]. These scenarios are detailed in Section B.3.8.3.

Current clinical management

In line with the approach for PFS and OS, the standard parametric distributions described in Section B.3.3.3 were fitted to ToT data for the GARNET-like cohort (N=[redacted]) in the UK RWE study. The AIC and BIC values for each of the extrapolations are summarised in Table 61. Extrapolations of ToT using each model up to five years are presented in Figure 55. It is assumed that by five years, all patients would have discontinued treatment with current clinical management, and therefore, consideration of longer-term extrapolations beyond five years is not required.

Table 61: Summary of goodness-of-fit statistics for current clinical management ToT – standard parametric and flexible models

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Standard parametric models				
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; RWE: real-world evidence; ToT: time on treatment; UK: United Kingdom.

Figure 55: Current clinical management ToT extrapolations up to five years

Abbreviations: ToT: time on treatment.

According to both AIC and BIC, the generalised gamma and gamma model provided the best fit to the observed ToT data from the UK RWE study. The generalised gamma model was therefore included in the base case cost-effectiveness analysis for ToT for the UK RWE.

Summary of base case extrapolations

The assumptions for ToT for dostarlimab and current clinical management in the base case cost-effectiveness analysis are presented in Table 62.

Table 62: A summary of the assumptions in the base case for ToT for dostarlimab and current clinical management

	Dostarlimab ToT extrapolation	Patients who continue to receive dostarlimab after [redacted]	Timepoint at which [redacted] discontinue dostarlimab	Current clinical management ToT extrapolation
Base case analysis	Log-logistic	[redacted]%	[redacted]	Generalised gamma

Abbreviations: ToT: time on treatment.

B.3.3.8 Adverse events

Dostarlimab

For AEs associated with dostarlimab, the incidence of any Grade 3 or 4 treatment-emergent AEs that occurred in ≥5% of patients were included in the model and derived from the GARNET trial (ITT population) – see Table 34 in Section B.2.8.2.

Current clinical management

AEs were not collected within the UK RWE study, and therefore AE data for the current clinical management comparator were not available.

AEs were identified in the published literature for each of the individual treatment regimens included as part of current clinical management in the base case cost-effectiveness analysis. The incidence of AEs for each treatment regimen were then assigned to each regimen, based on the weighting of each individual regimen as part of the current clinical management basket.

Initially, the trials identified within the clinical SLR were reviewed for published AE data. However, only the ZoptEC trial reported AE data in sufficient granularity (as part of the IPD obtained by GSK) to allow it to be used in the base case cost-effectiveness model. Therefore, a series of targeted literature searches were conducted in order to identify the best possible proxy AE data for the individual regimens included as part of current clinical management in other oncology indications with patient populations matching patients in GARNET as closely as possible. The sources that were identified and used to derive the AEs for the individual treatment regimens, and the patient population included in each study, are also detailed in Appendix P.2.

The AEs included within the base case cost-effectiveness analysis for dostarlimab and current clinical management are presented in Table 63. A summary of the AEs identified in the literature for each of the individual treatment regimens that make up current clinical management, or treatment regimens included in individual scenario analyses is presented in Appendix P.2.

Within the model, AEs were applied in the first model cycle, to reflect the assumption that events of high severity are most likely to be experienced during the initial phases of treatment. Disutilities and costs associated with AEs are described in Section B.3.4.4 and B.3.5.4, respectively.

Table 63: AE rates included within the base case cost-effectiveness analysis

Grade 3 or 4 treatment-emergent AEs occurring in ≥5% of patients	Dostarlimab	Current clinical management
Sample size	129	NA
Abdominal pain, %	[redacted]	0.0
Allergic reactions, %	[redacted]	2.8
Anaemia, %	[redacted]	4.1
Fatigue, %	[redacted]	3.8
Hand and foot syndrome, %	[redacted]	2.7
Leukopenia, %	[redacted]	1.3
Mucosal inflammation, %	[redacted]	0.8
Nausea, %	[redacted]	1.2
Neutropenia, %	[redacted]	24.8
Sensory neuropathy, %	[redacted]	2.2
Stomatitis, %	[redacted]	0.7
Thrombocytopenia, %	[redacted]	5.3

Vomiting, %	[redacted]	1.5
Investigation - Neutrophil count decreased, %	[redacted]	0.0
Investigation - White blood cell decreased, %	[redacted]	0.0
Source	GARNET (ITT population)	Appendix P.2

Footnote: The incidence of any Grade 3 or 4 TEAE that occurred in ≥5% of patients for each of the individual treatment regimens that make up current clinical management were included in the model. Once these AEs were subsequently re-weighted, some of the AEs were applied at a frequency of less than 5%.
Abbreviations: AE: adverse event; NA: not applicable; ITT: intention-to-treat.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

EQ-5D-5L data were collected in the GARNET trial, but only following protocol amendment 3, reducing the total number of patients included in the utility analysis. In total, 106 patients in the ITT population of GARNET had HRQoL data available at one or more timepoints and were included in the utility analysis.

The EQ-5D-5L data collected in GARNET were cross-walked to the EQ-5D-3L using the Van Hout *et al.* (2012) algorithm, in line with the most recent NICE position statement.[87, 98] The results of the cross-walk were subsequently valued using Dolan *et al.* (1997), which provides the standard UK EQ-5D-3L weights.[99]

A series of regression models were fitted to the cross-walked data to estimate the utility values. To account for the correlation between repeated measures from patients at separate timepoints, a generalised estimating equation approach was adopted, using pseudonymised patient identifiers to identify repeated sampling from individuals.

One of the covariates considered in the base case was progression status (pre- or post-progression). However, in addition to disease progression, there is a growing body of evidence which highlights that a patient's HRQoL declines substantially in the weeks and months prior to death.[88] As such, the regression model to predict utility values used in the base case analysis considered both disease progression and time to death. Time to death was modelled as a binary variable; patients were classified as "close to death" if they were ≤5 cycles from death; all other patients were classified as "not close to death". This threshold was selected to ensure that sufficient numbers of responses were included from patients "close to death", as alternative thresholds nearer to death resulted in extremely limited sample sizes.

In order to explore the impact of considering time-to-death as a covariate, a second regression model was also included in a scenario analysis, which only considered baseline utility and post- versus pre-progression, and excluded time to death as a covariate.

The health state utilities estimated by these regression models are presented in Table 64. Further details of these regression models are provided in Appendix P.5, including the baseline utility values.

Table 64: Health state utility values predicted from GARNET

Health state	Utility values
	Base case (including time to death)

Pre-progression (>5 cycles from death)	[redacted]
Pre-progression (≤5 cycles from death)	[redacted]
Post-progression (>5 cycle from death)	[redacted]
Post-progression (≤5 cycle from death)	[redacted]

B.3.4.2 Mapping

As EQ-5D data were available directly from the GARNET trial, no further mapping was required.

B.3.4.3 Health-related quality-of-life studies

A SLR was conducted to identify any published utility values estimated for patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy. Full details of the methodology and results of this SLR are presented in Appendix H.

As detailed in Appendix H.3, three publications were identified reporting utility values for patients with recurrent or advanced EC: Hildebrant *et al.* (2014), Lachance *et al.* (2008) and Stahl *et al.* (2018).[100-102]

The utility values reported in Hildebrant *et al.* (2014) have low validity: due to the limited applicability of German patient EQ-5D data to a UK setting, the small sample size present in the study (N=20) meaning there is limited data to inform health state utility values required for an oncology model.[100] Additionally, there is a paucity of data to distinguish between advanced patients who have and have not received previous treatment with platinum-based chemotherapy.[100]

The reported utility values in Lachance *et al.* (2008) were elicited from nine clinical experts. In addition to concerns with the small sample size of experts, there were limited details reported concerning the methods of expert recruitment, and how the elicitation exercise were conducted.[101] These same utility values were also used in the third publication that was identified: Stahl *et al.* (2018).[102]

Given the limitations associated with the published utility values identified in the economic SLR, the utility values derived from GARNET were preferred for the cost-effectiveness analyses presented in this submission, as outlined above.

B.3.4.4 Adverse reactions

The rates of AEs for patients on dostarlimab and relevant comparators in the model are detailed in Section B.3.3.8.

The impact of AEs on HRQoL was incorporated by applying a one-off utility decrement for each AE. Utility decrements were applied on an absolute (rather than relative) basis and applied in the first model cycle. Whilst the application of AE disutilities may be considered double-counting, it was considered important to capture the additional disutility associated with AEs experienced by patients receiving current clinical management, given the toxicity associated with chemotherapy.

The toxicity associated with chemotherapy is not captured in the pre-progression health state utility values, as these were derived from patients receiving dostarlimab in GARNET and then applied to patients receiving dostarlimab and current clinical management in the base case cost-

effectiveness analysis. The impact of excluding these disutilities was explored in a scenario analysis (Section B.3.8.3).

Additionally, the frequency at which the HRQoL data were collected in the GARNET trial was not sufficient enough to necessarily capture all the utility decrements resulting from AEs for patients receiving dostarlimab.

Due to the paucity of data for patients with EC in the literature, AE disutility estimates were informed by published evidence applied in gynaecological cancer NICE TAs and were validated with UK clinical experts. The utility decrements used in the base case cost-effectiveness analysis are detailed in Table 65.

Table 65: Adverse event disutilities

Adverse event	Disutility	Source
Abdominal pain	−0.069	NICE TA620[103] (Doyle *et al.* [2008][104] assumed the same as pain)
Allergic reactions	−0.116	Assumed equal to hand and foot syndrome
Anaemia	−0.119	NICE TA620[103] (Swinburn *et al.* [2010][105])
Fatigue	−0.073	NICE TA620[103] (Nafees *et al.* [2008][106])
Hand and foot syndrome	−0.116	Lloyd *et al.* (2006)[107]
Leukopenia	−0.090	Assumed equal to neutropenia
Mucosal inflammation	−0.151	Assumed equal to stomatitis
Nausea	−0.045	NICE TA528[108]
Neutropenia	−0.090	NICE TA620[103] (Nafees *et al.* [2008])
Sensory neuropathy	−0.116	Assumed equal to hand and foot syndrome
Stomatitis	−0.151	Lloyd *et al.* (2006)[107]
Thrombocytopenia	−0.090	Assumed equal to neutropenia
Vomiting	−0.103	Lloyd *et al.* (2006)[107]
Investigations		
Investigation: white blood cell decreased	0.000	Assumed to have no utility impact
Investigation: neutrophil count decreased	0.000	Assumed to have no utility impact

Abbreviations: NICE: National Institute for Health and Care Excellence; TA: technology appraisal.

B.3.4.5 Age-adjusted utility values

Utility decrements associated with age were derived using regression coefficient published by Ara and Brazier (2010).[109]

$$Utility = 0.9508566 + (0.02121216 \times male) - (0.000259 \times age) - (0.000033 \times age^2)$$

The above equation provides estimates of EQ-5D utility scores for adults in the general population by age and gender. To equate these estimates to the EC population, the proportional reduction in utility at each age relative to model baseline age was calculated and applied to the health state utility estimates on a multiplicative basis in the base case cost-effectiveness

analysis. A scenario analysis was conducted where age-adjusted utility values were not applied.

B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the utility values used in the base case cost-effectiveness analysis is presented in Table 66.

Table 66: Summary of utility values used in the base case cost-effectiveness analysis

Model health state	Utility value	Reference in submission	Justification
Health states			
Pre-progression (>5 cycles from death)	[redacted]	Section B.3.4.1	EQ-5D-5L utility values collected in GARNET and cross-walked to EQ-5D-3L. There is a growing body of evidence which highlights that a patient's HRQoL declines substantially in the weeks and months prior to death.[88] As such, baseline utility, disease progression and time to death were considered as covariates in the base case utility analysis.
Pre-progression (≤5 cycles from death)	[redacted]	Section B.3.4.1	
Post-progression (>5 cycle from death)	[redacted]	Section B.3.4.1	
Post-progression (≤5 cycles from death)	[redacted]	Section B.3.4.1	
Adverse events			
Abdominal pain	−0.069	Section B.3.4.4	Whilst the application of AE disutilities may be considered double-counting, it was considered important to capture the additional disutility associated with AEs experienced by patients receiving current clinical management given the toxicity associated with chemotherapy. The impact of including these disutilities was explored in a scenario analysis, whereby the inclusion of these AE disutilities was removed (see Section B.3.8.3).
Allergic reactions	−0.116	Section B.3.4.4	
Anaemia	−0.119	Section B.3.4.4	
Fatigue	−0.073	Section B.3.4.4	
Hand and foot syndrome	−0.116	Section B.3.4.4	
Leukopenia	−0.090	Section B.3.4.4	
Mucosal inflammation	−0.151	Section B.3.4.4	
Nausea	−0.045	Section B.3.4.4	
Neutropenia	−0.090	Section B.3.4.4	
Sensory neuropathy	−0.116	Section B.3.4.4	
Stomatitis	−0.151	Section B.3.4.4	
Thrombocytopenia	−0.090	Section B.3.4.4	
Vomiting	−0.103	Section B.3.4.4	
Investigation: white blood cell decreased	0.000	Section B.3.4.4	
Investigation: neutrophil count decreased	0.000	Section B.3.4.4	

Abbreviations: EQ-5D-5/3L: EuroQoL-5 dimensions-5/3 levels; HRQoL: health-related quality of life.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The economic analysis was conducted from an NHS and personal social services (PSS) perspective and therefore only included costs that would be incurred by the NHS and PSS.

Appropriate sources of unit costs, such as NHS reference costs 2018/19, the British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) costs, and the electronic Marketing Information Tool (eMIT) were used to inform the cost inputs in the model.[110-113] In the absence of any additional sources of evidence, assumptions were made where necessary for specific cost/resource inputs included in the model and validated through discussions with UK clinical experts.

A SLR was conducted to identify cost and resource use data for adult patients with recurrent or advanced EC. Full details of the search strategy, study selection process and results are presented in Appendix I.

The SLR identified 2,902 publications, of which 250 were selected for full review. Seven publications (five unique studies) reporting relevant cost and resource use data were identified in patients with recurrent or advanced EC. However, the cost and resource use reported in these publications provided limited data on unit costs, treatment costs and AE costs and were therefore not considered further for inclusion within the economic analysis.

B.3.5.1 Intervention and comparator drug acquisition costs and resource use

Drug acquisition costs for dostarlimab and the relevant comparator treatments comprising current clinical management were derived from the BNF for branded therapies and the eMIT for generic therapies, based on the dosing regimens for each therapy as detailed in Section B.3.2.3 (Table 48). Where required, mean patient characteristics from GARNET were used to calculate appropriate doses as detailed in Section B.3.3.1 (Table 49).

For current clinical management, drug acquisition costs were based on a weighted average of the individual treatment regimens that were received by ≥5% of patients in the GARNET-like cohort of the UK RWE study, in addition to hormone therapy, as detailed in Section B.3.2.3. The inclusion of individual treatment regimens that were received by ≥5% of patients only applies to the treatment acquisition costs and AEs – the efficacy is derived from the aggregate of all patients in the UK RWE GARNET-like cohort, regardless of the treatments that they received. This approach was validated by an independent health economist expert and was considered reasonable given it covered the treatments received by >75% of patients in the UK RWE study, and the treatments specified in the NICE scope.

For hormone therapy, drug acquisition costs were based on a weighted average (50:50) of the costs for medroxyprogesterone and letrozole, which was based on feedback from UK clinical experts that these hormone therapies would be the most commonly used in patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or following prior treatment with a platinum-containing regimen in UK clinical practice. Given the difference in costs between different hormone therapies is small, it was not considered that this assumption would have a large impact on results, but a scenario analysis was conducted assuming 100% of patients receiving hormone therapy received letrozole, given this is the cheaper of the two, as a conservative scenario.

The list prices for the comparator therapies were taken from either the eMIT (for therapies available to the NHS as generic medicines) or the BNF.[111, 113] The costs associated with each treatment regimen are detailed in Table 67.

In the base case cost-effectiveness analysis, PLD is the only form of doxorubicin included, as

PLD was the only form of doxorubicin received by ≥5% of patients in the UK RWE study. This is aligned with UK clinical expert opinion, which indicated that PLD would be the predominant form of doxorubicin used in UK clinical practice and that doxorubicin monotherapy ("naked" doxorubicin) is rarely used. However, in a scenario analysis, an individual comparison was conducted versus doxorubicin monotherapy, where doxorubicin monotherapy cost was comprised of a weighted average of [redacted]% "naked" doxorubicin monotherapy and [redacted]% PLD, in line with the proportions of patients receiving each treatment in the UK RWE study.

Table 67: Drug acquisition unit costs for dostarlimab and relevant comparators

Treatment regimen	Specific treatment	Vial/pack size	Cost per vial/pack	Required dosage (irrespective of vial size)	No. of vials/packs required per 21-day cycle	Cost per cycle per individual regimen (without vial sharing)	Total cost per cycle (including all treatments in regimen)	Cost source
Dostarlimab								
Dostarlimab monotherapy	Cycles 1–4	500 mg	£[redacted] (list price) £[redacted] (PAS price)	500 mg Q3W	1	£[redacted] (list price) £[redacted] (PAS price)	£[redacted] (list price) £[redacted] (PAS price)	GSK Data on File
	Cycles 5+			1,000 mg Q6W	0.5	£[redacted] (list price) £[redacted] (PAS price)	£[redacted] (list price) £[redacted] (PAS price)	
Current clinical management								
Carboplatin monotherapy	Carboplatin	150 mg	£6.03	501 mg Q4W (AUC 5)	0.75	£14.84	£14.84	eMIT[113]
		450 mg	£13.76		0.75			
Paclitaxel monotherapy	Paclitaxel	150 mg	£12.41	143 mg QW	3	£37.23	£37.23	eMIT[113]
PLD monotherapy	PLD	50 mg	£712.49	72 mg Q4W	1.5	£1,068.74	£1,068.74	BNF[114]
Carboplatin plus paclitaxel	Carboplatin	As per carboplatin monotherapy					£36.91	eMIT[113]
	Paclitaxel	30 mg	£4.41	313 mg Q3W	1	£22.07		eMIT[113]
		300 mg	£17.66		1			
Carboplatin plus PLD	Carboplatin	As per carboplatin monotherapy					£1,083.57	eMIT[113]
	PLD	As per PLD monotherapy						BNF[114]

Hormone therapy[a]	Medroxy-progesterone acetate	30 × 400 mg	£58.67	400 mg QD	0.7	£41.07	£21.12[a]	BNF[115]
	Letrozole	28 × 2.5 mg	£1.56	2.5 mg QD	0.75	£1.17		eMIT[113]
Individual chemotherapy regimens not listed above considered in scenario analyses only								
Doxorubicin monotherapy[b]	Doxorubicin	10 mg	£2.55	107 mg Q3W	1	£15.69	£830.55[b]	eMIT[113]
		50 mg	£6.57		2			
	PLD	As per PLD monotherapy						BNF[114]
Treatment regimens included as subsequent treatments[c, d] only (base case and scenario analyses)								
Gemcitabine monotherapy[c]	Gemcitabine	1,000 mg	£13.09	1,790 mg QW for three out of every four weeks	4.5	£58.91	£58.91	eMIT[113]
Bevacizumab[c]	Bevacizumab	400 mg	£831.96	1138 mg Q3W	3	£2,495.88	£2,495.88	BNF[116]
Carboplatin plus gemcitabine	Carboplatin	450 mg	£13.76	401 mg Q3W (AUC 4)	1	£13.76	£66.12	eMIT[113]
	Gemcitabine	1,000 mg	£13.09	1,790 mg QW for two out of every three weeks	4	£52.36		eMIT[113]

Footnotes: [a] Hormone therapy is considered as a weighted average (50:50) of medroxyprogesterone acetate and letrozole, in line with UK Clinical expert opinion. [b] In a scenario analysis, doxorubicin monotherapy cost was modelled as a weighted average of [redacted]% of patients receiving "naked" doxorubicin monotherapy and [redacted]% of patients receiving PLD monotherapy, based on the proportions of patients receiving each treatment in the UK RWE study. [c] Gemcitabine monotherapy and bevacizumab were only included in the economic analysis as subsequent treatments in a scenario analysis where patients receiving dostarlimab received subsequent treatments in line with those received in GARNET (Section B.3.8.3). [d] Radiotherapy was also included as a subsequent treatment – details of the costs associated with radiotherapy are presented in Section B.3.5.5, Table 71.
Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; PAS: patient access scheme; PLD: pegylated liposomal doxorubicin; QD: once daily; QXW: once every X weeks.

B.3.5.2 Drug administration costs

Dostarlimab and all of the chemotherapy regimens considered in the base case cost-effectiveness analysis are administered via intravenous (IV) infusion and were assumed to be associated with administration costs based on NHS reference costs 2018/2019. An overview of the relevant drug administration costs applied within the model is presented in Table 68.

At the first attendance visit, all monotherapy chemotherapy regimens were assumed to incur a simple administration cost, whilst combination regimens incurred a complex administration cost for the first attendance visit. All subsequent administrations were then assigned the same cost for the administration of subsequent elements of a chemotherapy cycle.

Oral therapies, including medroxyprogesterone and letrozole, were not assumed to be associated with any administration costs.

Table 68: Drug administration costs

Drug	Cost	Source/Assumptions
IV simple administration – first attendance	£241.06	NHS reference costs 2018/19: SB12Z deliver simple parenteral chemotherapy at first attendance (total HRGs)[110]
IV complex administration – first attendance	£306.90	NHS reference costs 2018/19: SB13Z deliver more complex parenteral chemotherapy at first attendance[110]
IV subsequent administration	£332.13	NHS reference costs 2018/2019: SB15Z deliver subsequent elements of a chemotherapy cycle[110]

Abbreviations: HRG: Healthcare Resource Group; IV: intravenous; NHS: National Health Service; PSSRU: Personal Social Services Research Unit.

B.3.5.3 Follow-up and monitoring costs and resource use

The economic SLR (described in Section B.3.5) did not identify any previous economic evaluations, UK cost studies or NICE appraisals for recurrent or advanced EC that could help inform follow-up and monitoring costs associated with patients with recurrent or advanced EC within the economic model.

As such, interviews were conducted with UK clinical experts to determine the resource use that might be expected to be associated for patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy, according to disease progression status and the treatments received.[16] The resource use estimates based on the clinical expert feedback are summarised in Table 69, and were applied independent of treatment received. Unit costs were taken from NHS reference costs 2018/2019 and the PSSRU where appropriate.[110, 112]

Table 69: Routine care and monitoring unit costs

Resource			Number of units per 3-week model cycle[a]			Total cost per 3-week model cycle		
	Unit cost	Source	Pre-prog on treatment[b]	Pre-prog off treatment[b]	Post-prog	Pre-prog on treatment[b]	Pre-prog off treatment[b]	Post-prog
Secondary care								
Outpatient visit (consultant oncologist) – first	£267.65	NHS reference costs 2018/2019 (503, gynaecological oncology; outpatient procedures, WF01B non-admitted face-to-face attendance, first)[110]	1.00	0.00	0.00	£267.65	£0.00	£0.00
Outpatient visit (consultant oncologist) – follow-up	£176.45	NHS reference costs 2018/2019 (503, gynaecological oncology; outpatient procedures, WF01A non-admitted face-to-face attendance, follow-up)[110]	1.00	0.30	0.30	£176.45	£52.94	£52.94
Blood test (Full blood count)	£2.79	NHS reference costs 2018/2019 (total other currencies, DAPS05 haematology)[110]	1.00	0.30	0.30	£2.79	£0.84	£0.84
CT scan	£97.15	NHS reference costs 2018/2019 (total HRGs, weighted average of RD20A, CT scan of one area, without contrast, 19 years and over, RD21A, CT scan of one area, with post-contrast only, 19 years and over, RD22Z–RD27Z, CT scan of one area with pre- and post-contrast–CT scan of more than three areas[c]) [110]	0.30	0.30	0.30	£29.15	£29.15	£29.15

Resource			Number of units per 3-week model cycle[a]			Total cost per 3-week model cycle		
Specialist nurse	£50.00	PSSRU 2020 (hospital-based health care staff: hospital-based nurses, assumed Band 6; cost per hour of patient contact, assumed as one hour)[110]	1.00	1.00	1.00	£50.00	£50.00	£50.00
GP visit	£39.00	PSSRU 2020 (community-based health care staff: general practitioner, with qualification costs, assumed as a 9.22-minute appointment [duration])[110]	1.00	1.00	1.00	£39.00	£39.00	£39.00
Nurse visit	£48.00	PSSRU 2020 (community-based health care staff: nurses, assumed Band 6; cost per hour of patient contact, assumed as one hour)[110]	0.30	0.30	0.30	£14.40	£14.40	£14.40
Total								
First cycle total	NA	NA	NA	NA	NA	£402.99	NA	NA
Follow-up cycle total	NA	NA	NA	NA	NA	£311.79	£186.32	£186.32

Footnotes: [a] The number of units per three week model cycle were informed by UK clinical expert opinion. [b] 'On-treatment' was defined as a patient in the post platinum follow-up period that has not progressed on their next treatment. 'Off-treatment' was defined as a patient in the post platinum follow-up period that has been on their next treatment for a maximum of two years and has not progressed within this time. [c] The CT scan codes were weighted assuming: 0.3 scans (on-treatment patients pre-progression); 0.3 scans (off-treatment patients pre-progression); 0.3 scans (on-treatment patients post-progression); 0.3 scans (off-treatment patients post-progression);
Abbreviations: CT: computerised tomography; FBC: full blood count; GP: general practitioner; HRG: Healthcare Resource Group; NA: not applicable; NHS: National Health Service; PSSRU: Personal Social Services Research Unit.

B.3.5.4 Adverse event costs and resource use

TEAEs of grade 3 or above were included into the economic model if they occurred in ≥5% of dostarlimab patients in the ITT population of the GARNET trial at the time of the interim analysis (DCO 1st March 2020, detailed in Section B.2.8.2, Table 34 and Section B.3.3.8) or ≥ 5% of the patients receiving any of the individual regimens that make up the current clinical management based on published literature.[6, 59] AE rates included within the model for dostarlimab and the relevant comparators are summarised in Section B.3.3.8.

Cost estimates for the treatment of each AE were derived from NHS reference costs 2018/19 and are summarised in Table 70.[110] It was assumed that each AE was only experienced once per patient, and the cost of each AE was applied within the first cycle of the model.

Table 70: AE costs

AE	Cost estimate	Source/assumptions
Abdominal pain	£375.46	NHS reference costs 2018/19. Weighted average of non-elective short stage FD05A (0.1%) and FD05B (99.9%); non-elective short stays with or without interventions).[110] *Method as applied in NICE TA620.*[103]
Allergic reaction and hand and foot syndrome	£404.26	NHS reference costs 2018/19.[110] Weighted average of non-elective short stay JD07A (0.1%), JD07B (0.1%), JD07C (0.1%), JD07D (0.6%), JD07E (0.8%), JD07F (3.8%), JD07G (8.4%), JD07H (17.1%), JD07J (33.2%), JD07K (35.8%); skin disorders with interventions with CC Score 12+, 8–11, 4–7, 0–3, and skin disorders without interventions with CC Score 19+, 14–18, 10–13, 6–9, 2–5, 0–1, respectively.[110]
Anaemia	£485.28	NHS reference costs 2018/19. Weighted average of non-elective short stay SA04G (6.2%), SA04H (12.1%), SA04J (23.7%), SA04K (35.9%) and SA04L (22.1%); non-elective short stay for iron deficiency anaemia with CC score 14+, 10–13, 6–9, 2–5 and 0–1, respectively.[110] *Method as applied in NICE TA620.*[103]
Fatigue	£0	Assumption as per NICE TA620.[103]
Leukopenia and neutropenia	£431.19	NHS reference costs 2018/19. Weighted average of non-elective short stays SA08G (23.6%), SA0GH (24.7%) and SA08J (51.7%); other haematological or splenic disorders with CC Score 6+, CC Score 3–5 and CC Score 0–2, respectively.[110] *Method as applied in NICE TA620.*[103]
Mucosal inflammation and stomatitis	£391.93	NHS reference costs 2018/19. Weighted average of non-elective short stays CB02A (0.4%), CB02B (0.7%), CB02C (0.4%), CB02D (30.8%), CB02E (42.7%) and CB02F (24.9%), non-malignant, ear, nose, mouth, throat or neck disorders with interventions with CC Score 5+, 1–4 and 0, and without interventions with CC Score 5+, 1–4 and 0, respectively.[110]
Nausea and vomiting	£447.58	Assumed to require one hospital admission, consisting of: NHS reference costs 2018/2019 (index, unit cost for regular day or night admissions) *and ;*NHS reference costs 2018/19[110] (total other currencies, N16AF, specialist nursing – enteral feeding nursing services, adult, face-to-face).[110] *Method as applied in NICE TA611.*[117]
Sensory neuropathy	£351.03	NHS reference costs 2018/19. [110 110 110 107] Weighted average of non-elective short stays WHO8A (39.5%) and WH08B (60.5%); Unspecified with CC Score 1+ and 0, respectively.[110]

Thrombocytopenia	£655.62	NHS reference costs 2018/19. Weighted average of: Non-elective long stay SA12G (4.2%), SA12H (2.3%), SA12J (3.0%) and SA12K (1.6%); Non-elective short stay SA12G (2.7%), SA12H (2.8%), SA12J (4.6%) and SA12K (4.1%); Day case SA12G (4.0%), SA12H (6.4%), SA12J (20.2%) and SA12 (29.4%); Regular day and night SA12G (0.9%), SA12H (1.4%), SA12J (4.9%) and SA12K (7.4%); thrombocytopenia with CC Score 8+, CC Score 5–7, CC Score 2–4 and CC Score 0–1, respectively.[110] *Method as applied in NICE TA611.*[117]
Investigation – white blood cell decreased	£220.69	NHS reference costs 2018/19. Total HRGs RN13Z, nuclear medicine infection scan or white cell scan.[110]
Investigation – neutrophil count decreased	£220.69	Assumed equivalent to investigation – white blood cell decreased.

Abbreviations: AE: adverse event; CC: complexity and comorbidity; HRG: Healthcare Resource Group; NHS: National Health Service; NICE: National Institute for Health and Care Excellence.

B.3.5.5 Subsequent therapies costs and resource use

The base case economic analysis also included the costs of subsequent therapies that might be received by patients upon progression from treatment with dostarlimab or the relevant comparators. The proportion of patients that received subsequent therapies and the treatment regimens received by patients following dostarlimab or current clinical management are detailed in Section B.3.2.3.

Whilst subsequent therapies were captured within the GARNET trial, it was not considered that these would be representative of the treatments that might be received in clinical practice, and particularly following current clinical management, as detailed in Section B.3.5.5. As such, in the base case cost-effectiveness analysis, the subsequent therapies received following treatment with dostarlimab and current clinical management, and the average duration of treatment associated with the subsequent therapies received, were based on the UK RWE study for patients receiving 2L and 3L treatment, respectively, given the longer follow-up of data available and that the data were derived from the UK.

A summary of the treatment costs per cycle for each of the subsequent treatment regimens is presented in Table 71, based on the costs calculated in Table 67. The mean subsequent treatment costs for all cycles for patients that received dostarlimab or current clinical management are shown in Table 72.

As detailed in Section B.3.2.4, a scenario analysis was also conducted where patients who received dostarlimab received the subsequent treatments recorded in the GARNET trial; the associated costs are detailed in Table 72, and the associated proportions for each subsequent therapy are presented in Appendix P.1. Pembrolizumab was received following dostarlimab by [redacted]% of patients in the GARNET trial. As pembrolizumab is not currently available on the NHS for patients with EC, pembrolizumab was removed from the calculations and the remaining subsequent therapies were re-weighted accordingly.

Table 71: Subsequent therapy costs included within the model

Drug	Cost per cycle	Cost source	Number of cycles of subsequent treatment (following dostarlimab)	Number of cycles of subsequent treatment (following current clinical management)	Duration of treatment source
Carboplatin plus paclitaxel	£36.91	Table 67	[redacted]	[redacted]	GSK Data on File (calculated from the median ToT from the UK RWE study)[b]
Paclitaxel monotherapy	£37.23	Table 67	[redacted]	[redacted]	GSK Data on File (calculated from the median ToT from the UK RWE study)[b]
Carboplatin plus PLD	£1,083.57	Table 67	[redacted]	[redacted]	GSK Data on File (calculated from the median ToT from the UK RWE study)[b]
PLD monotherapy	£1,068.74	Table 67	[redacted]	[redacted]	GSK Data on File (calculated from the median ToT from the UK RWE study)[b]
Carboplatin monotherapy	£14.84	Table 67	[redacted]	[redacted]	GSK Data on File (calculated from the median ToT from the UK RWE study)[b]
Carboplatin plus gemcitabine	£66.12	Table 67	[redacted]	[redacted]	GSK Data on File (calculated from the median ToT from the UK RWE study)[b]
Hormone therapy	£21.12[a]	Table 67	4.64	4.64	PARAGON[74] (calculated from the published median ToT estimate)
Gemcitabine monotherapy	£58.91	Table 67	[redacted]	[redacted]	GSK Data on File (calculated from the median ToT from the UK RWE study)[b]
Doxorubicin monotherapy	£15.69	Table 67	[redacted]	[redacted]	GSK Data on File (calculated from the median ToT from the UK RWE study)[b]

Bevacizumab monotherapy	£2,495.88	Table 67	[redacted]	[redacted]	GSK Data on File (calculated from the median ToT from the UK RWE study)[b]
Radiotherapy	£2,722.78	NHS reference costs 2018/2019 (total HRGs, SC55Z, preparation for interstitial brachytherapy and SC28Z, deliver a fraction of interstitial brachytherapy)	8.70	8.70	Fackrell *et al.* (2012)[118] (calculated from the median duration of palliation)

Footnotes: [a] Hormone therapy is considered as a weighted average of medroxyprogesterone acetate and letrozole, in line with UK Clinical expert opinion. [b] Subsequent therapies and duration of subsequent therapy treatment for patients receiving dostarlimab and current clinical management were based on the therapies (and median duration of therapy) received in the 2L and 3L of the UK RWE study, respectively (Section B.3.5.5 and Appendix P.1). Median time on treatment was [redacted] months (corresponding to [redacted] model cycles) in the 2L and [redacted] months (corresponding to [redacted] model cycles) in the 3L. [c] The number of subsequent cycles of hormone therapy was based on the median ToT estimate of 3.2 months in the PARAGON study, corresponding to 4.64 model cycles. [d] The number of subsequent cycles of radiotherapy was calculated based on the median duration of palliation of 6 months (corresponding to 8.70 model cycles).
Abbreviations: PLD: pegylated liposomal doxorubicin.

The proportion of patients who received subsequent therapy after treatment with dostarlimab and current clinical management in the base case cost-effectiveness analysis is described in Section B.3.2.4. The total costs of subsequent therapies for each arm is presented in Table 76. A scenario analysis whereby patients who received dostarlimab were assumed to receive subsequent therapies as per those received in the GARNET trial is presented in Section B.3.8.3

Table 72: Total subsequent therapy costs in the base case cost-effectiveness analysis

	Dostarlimab[a]	Current clinical management[b]
Mean subsequent treatment acquisition costs across all cycles	£3,010.86	£2,883.12

Footnotes: [a] Based on the subsequent treatment distribution for patients receiving 2L treatment in the UK RWE study (Section B.3.5.5 and Appendix P.1); [b] Based on the subsequent treatment distribution for patients receiving 3L treatment in the UK RWE study (Section B.3.5.5 and Appendix P.1).
Abbreviations: 2L: second-line; 3L: third-line; RWE: real-world evidence; UK: United Kingdom.

B.3.5.6 End-of-life costs and resource use

Costs for end-of-life care were included for all patients who experienced mortality events in the model and were applied as a one-off cost during the model cycle prior to death. The costs of end-of-life care were assumed to be £8,104.88 based on a previous 2016 publication in ovarian cancer inflated to 2018/2019.

Table 73: End-of-life care costs

Cost estimate	Source/description
£8,104.88	Guest *et al.* (2006)[119] estimated the costs of palliative care associated with ovarian cancer to be £4,789 (2000/2001 UK setting). Given a lack of direct evidence for palliative care costs for EC, this estimate was considered to be the most relevant proxy. This approach was used in TA598[120], where this estimate was inflated from the 2000/2001 to 2016/2017 UK cost setting, resulting in an estimate of £7,638.51. This value of £7,638.51 has now been inflated to the 2019/2020 UK cost setting using the PSSRU 2016/2017 to 2019/2020 inflation indices (1.0210 and 1.0833, respectively), resulting in an estimate of £8,104.88

Abbreviations: HTA: health technology assessment; NHSCII: National Health Service Cost Inflation Index; PSSRU: Personal Social Services Research Unit; UK: United Kingdom.

B.3.5.7 Diagnostic testing costs and resource use

NICE diagnostic guidance DG42 recommends that all patients with EC should be tested using IHC to identify tumours with dMMR.[18] As such, dMMR testing will soon become standard of care for all patients with EC and dMMR testing costs were not included within the base case economic analysis. NHS England confirmed the widespread availability of dMMR testing in England and Wales during an NHS surgery consultation in March 2021 (Section B.1.3.2).

In order to explore the impact of including the costs for dMMR testing within the economic model, a scenario analysis was conducted whereby the cost of dMMR testing was applied to all patients who enter the model with recurrent EC: 42% of patients.

Whilst it is not anticipated that dMMR testing will be required as an additional test based on the recent NICE DG42 guidance to conduct IHC testing as standard, it is acknowledged that some

recurrent EC patients may not have received dMMR testing at diagnosis and therefore this has been explored within a scenario analysis.

The cost of each dMMR test is presented in Table 74. The sensitivity and specificity of IHC testing is presented in Table 75.

Table 74: Number of patients requiring IHC testing for dMMR (considered in a scenario analysis only)

	Dostarlimab	Comparators	Source
	Value	Value	
Proportion of patients untested at baseline	100%	100%	Assumption
Prevalence of dMMR (MLH1, MSH2, MSH6, PMS2)	23%	23%	NICE DG42[18]
Eligibility conditional on MMR deficiency	Yes	Yes	NA
Number needed to test per eligible patient	1.00	1.00	NA
IHC testing cost applicable per treated patient	£210.00	0.00	NICE DG42[18]

Abbreviations: dMMR: DNA mismatch repair deficient; IHC: immunohistochemistry; MLH1: MutL homolog 1; MSH2: MutS homolog 2; MSH6: MutS homolog 6; NA: not applicable; PMS2: mismatch repair endonuclease PMS2.

Table 75: IHC testing for determining MMR/MSI status – sensitivity and specificity and costs (considered in a scenario analysis only)

IHC testing	Value	Lower	Upper	Source
Cost	£210.00	NR	NR	NICE DG42[18]
Sensitivity	0.962	0.694	0.996	NICE DG27[44]
Specificity	0.884	0.79	0.94	NICE DG27[44]

Abbreviations: IHC: immunohistochemistry; MMR: DNA mismatch repair; MSI, microsatellite instability; NR: not reached.

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

A summary of the key base case model inputs is provided in Table 76.

Table 76: Summary of variables applied in the base case economic analysis

Variable	Value	Reference to section in submission
Model settings		
Cycle length	Three weeks	Section B.3.2.2
Time horizon	40 years	Section B.3.2.2
Discount rate (costs and outcomes)	3.5%	Section B.3.2.2
Patient characteristics		
Mean age, years	[redacted]	Section B.3.3.1

Mean height at baseline, cm	[redacted]	Section B.3.3.1
Mean weight at baseline, kg	[redacted]	Section B.3.3.1
Mean BSA, m^2	[redacted]	Section B.3.3.1
eGFR, mL/min	[redacted]	Section B.3.3.1
Clinical efficacy: dostarlimab		
PFS	Lognormal	Section B.3.3.5
OS	Generalised gamma	Section B.3.3.6
ToT	Log-logistic	Section B.3.3.7
Percentage of patients who continue dostarlimab after [redacted], %	[redacted]	Section B.3.3.7
Percentage of patients who continue dostarlimab after [redacted], %	[redacted]	Section B.3.3.7
Timepoint for start of treatment waning applied to PFS and OS	[redacted]	Section B.3.3.4
Timepoint for end of treatment waning applied to PFS and OS	[redacted]	Section B.3.3.4
Clinical efficacy: current clinical management		
PFS	Log-logistic	Section B.3.3.5
OS	Log-logistic	Section B.3.3.6
ToT	Generalised gamma	Section B.3.3.7
Adverse event frequency: dostarlimab		
Abdominal pain, %	[redacted]%	Section B.3.3.8
Anaemia, %	[redacted]%	Section B.3.3.8
AE frequency: current clinical management		
Allergic reactions, %	2.8	Section B.3.3.8
Anaemia, %	4.1	Section B.3.3.8
Fatigue, %	3.8	Section B.3.3.8
Hand and foot syndrome, %	2.7	Section B.3.3.8
Leukopenia, %	1.3	Section B.3.3.8
Mucosal inflammation, %	0.8	Section B.3.3.8
Nausea, %	1.2	Section B.3.3.8
Neutropenia, %	24.8	Section B.3.3.8
Sensory neuropathy, %	2.2	Section B.3.3.8
Stomatitis, %	0.7	Section B.3.3.8
Thrombocytopenia, %	5.3	Section B.3.3.8
Vomiting, %	1.5	Section B.3.3.8
Health state utility values		
Pre-progression (>5 cycles from death)	[redacted]	Section B.3.4.6
Pre-progression (≤5 cycles from death)	[redacted]	Section B.3.4.6
Post-progression (>5 cycle from death)	[redacted]	Section B.3.4.6
Post-progression (≤5 cycles from death)	[redacted]	Section B.3.4.6

AE disutilities		
Abdominal pain	−0.069	Section B.3.4.4
Allergic reactions, hand and foot syndrome and sensory neuropathy	−0.116	Section B.3.4.4
Anaemia	−0.119	Section B.3.4.4
Fatigue	−0.073	Section B.3.4.4
Leukopenia, neutropenia and thrombocytopenia	−0.090	Section B.3.4.4
Mucosal inflammation and stomatitis	−0.151	Section B.3.4.4
Nausea	−0.045	Section B.3.4.4
Vomiting	−0.103	Section B.3.4.4
Investigation: white blood cell decreased	0.000	Section B.3.4.4
Investigation: neutrophil count decreased	0.000	Section B.3.4.4
Drug acquisition: total costs per cycle		
Dostarlimab monotherapy: cycles 1–4	£[redacted] (list price) £[redacted] (PAS price)	Section B.3.5.2
Dostarlimab monotherapy: cycles 5+	£[redacted] (list price) £[redacted] (PAS price)	Section B.3.5.2
Carboplatin (monotherapy and in combination with paclitaxel or PLD)	£14.84	Section B.3.5.2
Paclitaxel (in combination with carboplatin)	£22.07	Section B.3.5.2
Paclitaxel monotherapy	£37.23	Section B.3.5.2
PLD (monotherapy and in combination with carboplatin)	£1,068.74	Section B.3.5.2
Hormone therapy (calculated as a weighted average of 50% medroxyprogesterone acetate and 50% letrozole in line with clinical expert opinion)	£21.12	Section B.3.5.2
Doxorubicin monotherapy (scenario analysis only: weighted average of [redacted]% doxorubicin and [redacted]% PLD in line with the UK RWE study)	£830.55	Section B.3.5.2
Drug administration		
IV simple administration – first attendance	£241.06	Section B.3.5.2
IV complex administration – first attendance	£306.90	Section B.3.5.2
IV subsequent administration	£332.13	Section B.3.5.2
Follow-up and monitoring unit costs		
Outpatient visit (consultant oncologist) – first	£267.65	Section B.3.5.3
Outpatient visit (consultant oncologist) – follow-up	£176.45	Section B.3.5.3
Blood test (Full blood count)	£2.79	Section B.3.5.3

CT scan	£97.15	Section B.3.5.3
Specialist nurse	£50.00	Section B.3.5.3
GP visit	£39.00	Section B.3.5.3
Nurse visit	£48.00	Section B.3.5.3
Adverse event costs		
Abdominal pain	£375.46	Section B.3.5.4
Allergic reaction and hand and foot syndrome	£404.26	Section B.3.5.4
Anaemia	£485.28	Section B.3.5.4
Fatigue	£0	Section B.3.5.4
Leukopenia and neutropenia	£431.19	Section B.3.5.4
Mucosal inflammation and stomatitis	£391.93	Section B.3.5.4
Nausea and vomiting	£447.58	Section B.3.5.4
Sensory neuropathy	£351.03	Section B.3.5.4
Thrombocytopenia	£655.62	Section B.3.5.4
Subsequent therapy costs (the costs for other subsequent therapies in the model are equal to the drug acquisition costs listed previously)		
Gemcitabine monotherapy	£58.91	Section B.3.5.1
Gemcitabine (in combination with carboplatin)	£52.36	Section B.3.5.1
Carboplatin (in combination with gemcitabine)	£13.76	Section B.3.5.1
Bevacizumab	£2,495.88	Section B.3.5.1
Doxorubicin monotherapy	£15.69	Section B.3.5.1
Letrozole monotherapy	£1.17	Section B.3.5.1
Radiotherapy	£2,722.78	Section B.3.5.1
End-of life costs		
End-of-life care	£8,104.88	Section B.3.5.6

Abbreviations: AE: adverse event; BSA: body surface area; CT: computerised tomography; GP: general practitioner; IV: intravenous; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; PLD: pegylated liposomal doxorubicin; RWE: real-world evidence; ToT: time on treatment; UK: United Kingdom.

B.3.6.2 Assumptions

A list of the assumptions used in the base case analysis to be provided in Table 77 alongside a list of scenarios conducted to explore the impact of these assumptions on the cost-effectiveness results.

Table 77: List of assumptions for the base case cost-effectiveness analysis

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
Modelling of PFS and OS for dostarlimab	The GARNET ITT population is assumed to provide efficacy data for PFS and OS for patients treated with dostarlimab.	The GARNET trial provides direct clinical evidence, including patients treated with dostarlimab who would be reflective of patients who would receive dostarlimab in UK clinical practice. The ITT population in GARNET represents the largest sample size, and therefore provides the most robust efficacy evidence for PFS and OS to present in the base case cost-effectiveness analysis.	No scenario analyses have been conducted using alternative sources of efficacy for dostarlimab.
	The treatment effect on PFS and OS for dostarlimab versus current clinical management is assumed to last completely for [redacted] after [redacted] discontinue treatment, and then treatment waning is applied for [redacted], until after [redacted] the efficacy of dostarlimab is assumed to be equal to the efficacy of current clinical management.	The application of a treatment waning assumption makes the analysis much more conservative. The generalised gamma curve has a fat tail and to align better with clinical opinion on the shape of the curve, it was considered that waning should be applied to this curve choice. This approach is aligned with past NICE appraisals for I-O therapies,[85, 86, 95, 96] and the treatment waning approach applied in the base case cost-effectiveness analysis was validated as appropriate by UK clinical experts.	Scenario analyses have been conducted where treatment waning begins at [redacted] and [redacted], [redacted] and [redacted] after the timepoint at which [redacted] discontinue treatment with dostarlimab. A scenario analysis has also been conducted where treatment waning is applied for [redacted] for PFS and [redacted] for OS.
Modelling of ToT for dostarlimab	[redacted]% of patients on dostarlimab will continue treatment beyond [redacted]	In the GARNET trial, patients were eligible for treatment with dostarlimab for up to two years. Patients were able to continue treatment beyond two years if the treating physician and the sponsor agreed that the patient was continued to benefit from dostarlimab.	Scenario analyses have been conducted where [redacted]% and [redacted]% of patients continue receiving treatment with

		UK clinical experts indicated that based on their clinical experience with other I-O therapies, they would expect the real-world percentage of patients treated with dostarlimab after [redacted] would likely be between [redacted]% and [redacted]%. None of the parametric models provided a good fit to the observed data during the within-trial period and predict clinically plausible longer-term extrapolations for the number of patients receiving dostarlimab after [redacted]. In order to account for the discrepancy, an adjustment was applied to the long-term extrapolation in order to reflect the anticipated real-world prescribing that would be associated with dostarlimab. This approach was aligned with the approach considered in NICE TA517,[84] where the clinical expert opinion stated that the majority of patients would discontinue treatment with avelumab, another I-O therapy, after [redacted]. The same assumption was also accepted in NICE TA691.[97]	dostarlimab after [redacted]
	There is a maximum treatment duration for patients treated with dostarlimab; [redacted] still on treatment after [redacted] are then assumed to discontinue treatment.	Based on clinical expert feedback, it is reasonable to assume that [redacted] would receive dostarlimab for longer than [redacted], therefore, [redacted] are assumed to discontinue treatment by this timepoint. A similar dichotomous treatment duration was considered appropriate for decision making in TA517,[84] where the company submission assumed that the majority of patients would discontinue treatment at [redacted], and the remaining patients would discontinue treatment at [redacted]. The committee agreed that this assumption was reflective of clinical practice. The same assumptions were also accepted as part of TA691.[97]	Scenario analyses have been conducted where [redacted] are assumed to discontinue treatment with dostarlimab after [redacted] and [redacted], respectively.
Modelling of PFS, OS and ToT for current clinical management	The UK RWE study provides efficacy data and ToT data for comparator treatments used as current clinical management in the UK	GSK conducted a UK RWE study, which provides comparative evidence for a large cohort of patients (N=[redacted]) generalisable to the population of interest in this appraisal. The UK RWE study was considered to be the most robust source of comparative efficacy evidence and is used in the base case cost-effectiveness analysis.	To explore uncertainty in the RWE OS estimate, two scenarios were included where the OS for current clinical management was calculated by applying the

			HR from the UK RWE MAIC (described in Section B.2.7.1 to the dostarlimab OS extrapolation. To explore the uncertainty between individual comparators, a series of pairwise ITCs were conducted for PFS and OS between dostarlimab and the individual chemotherapy comparators listed in the NICE final scope, based on published data identified in the clinical SLR: Pairwise scenarios were conducted versus doxorubicin monotherapy, paclitaxel monotherapy and carboplatin plus paclitaxel, based on the results of the ITCs described in Section B.2.7.1 and Section B.2.7.2. The efficacy for these individual chemotherapy comparators was derived by applying a HR calculated from the ITCs to the dostarlimab PFS or OS extrapolation.

			No data were identified for carboplatin monotherapy in the literature; a scenario was conducted where the efficacy of carboplatin monotherapy was assumed to be equal to doxorubicin monotherapy, based on the ITCs noted above. One scenario was conducted where the efficacy of hormone therapy was assumed to be equal to current clinical management in the UK RWE study, given the paucity of data for hormone therapy in the published literature. These scenarios, and the underlying assumptions, are detailed in Section B.3.8.3.
	The GARNET-like cohort of the UK RWE study, including patients with an ECOG performance status (PS) of not recorded (NR), is used in the base case cost-effectiveness analysis.	Patients with an ECOG PS of NR were included in the GARNET-like UK RWE cohort in order to retain a larger sample size of patients, and to allow for a longer-follow-up of data. An ECOG PS of ≤1 was a key inclusion criterion of the GARNET trial. However, It is likely that only a small minority of patients would have had an ECOG PS >1 if the PS of all patients had been known, given that the number of patients with an ECOG PS >1 only accounted for a small proportion of the overall RWE cohort.	A scenario analysis was explored where PFS, OS and ToT data for the UK RWE GARNET-like ECOG PS ≤1 cohort were used to provide evidence for current clinical management. The base case extrapolations

			for current clinical management for PFS (log-logistic) and OS (log-logistic) also provided the best statistical fit for the ECOG PS ≤1 cohort, so these werechosen as the long-term extrapolations for PFS and OS for the UK RWE GARNET-like ECOG PS ≤1 cohort. The generalised gamma extrapolation was the second best statistical fit for ToT for the ECOG PS ≤ 1 cohort, but given the close alignment with the Weibull extrapolation (the best statistical fit), the generalised gamma was chosen in this scenario analysis for consistency with the UK RWE GARNET-like cohort extrapolations used in the base case cost-effectiveness analysis. These extrapolations are detailed in Appendix P.4.
	TTNT was used as a conservative proxy for PFS given that it was not possible to obtain PFS from the UK RWE study.	UK clinical expert opinion indicated that using TTNT rather than PFS is likely to be a conservative assumption in that it overestimates the PFS associated with current clinical management, given that patients will likely experience a delay between	A scenario analysis has been conducted where TTD from the UK RWE study is used as a proxy for PFS,

		disease progression and the initiation of their next line of therapy.	instead of TTNT.
Utility values	The utility values used in the base case cost-effectiveness analysis assumed a lower utility value for patients within 5 cycles of death.	This assumption was based on a growing body of evidence which highlights that a patient's HRQoL declines substantially in the weeks and months prior to death,[88] and aligns with an accepted assumption adopted in TA520.[86]	A scenario analysis was conducted whereby pre and post progression utilities have instead been applied and time to death was excluded as a covariate in the utility regression analysis.
Composition of current clinical management	The costs associated with current clinical management were based on a weighted average of the individual treatment regimens that were received by ≥5% of patients in the GARNET-like cohort of the UK RWE study plus hormone therapy	The inclusion of individual treatment regimens that were received by ≥5% of patients only applies to the treatment acquisition costs – the efficacy for current clinical management in the UK RWE GARNET-like cohort is derived from the aggregate of all patients in the UK RWE GARNET-like cohort, regardless of the treatments that they received. The costing approach was validated by an independent health economist expert and was considered reasonable given it covered the treatments received by the majority of patients in the UK RWE study and aligns with the treatments specified in the NICE scope. The independent health economist indicated that this approach would not introduce any bias into the analysis.	No scenario analyses were conducted to explore this assumption as it was not considered that the inclusion of further chemotherapy regimens received by small numbers of patients in clinical practice would have a large impact on the base case cost-effectiveness results.
	20% of patients receiving current clinical management are assumed to receive hormone therapy. This assumption also implicitly assumes that the efficacy of hormone therapy is equal to that of chemotherapy.	Hormone therapy was listed in the scope as a relevant comparator. Unfortunately, the RWE study, because of the way the data collection occurs, was unable to capture widespread use of hormone therapy. The UK clinical experts indicated that survival with hormone therapy would not be expected to exceed that observed in the UK RWE study: Median PFS and OS for hormone therapy in this setting would be ~ 3 months and ~ 6 months, respectively, whereas median PFS from the UK RWE study is [redacted] months and median OS is [redacted] months.	Scenario analyses have been conducted where 0%, 10%, 30% and 100% of patients receive hormone therapy as part of current clinical management. In the absence of any alternative data sources for hormone therapy, no scenarios

		As such, a pragmatic solution to resolve the missing hormone therapy data, was to weight the RWE basket to account for hormone therapy on the cost side and expert opinion was sought to understand the proportion of hormone therapy used in this setting. Clinical expert opinion indicated that approximately 20% of patients receiving treatment for recurrent or advanced EC following platinum-based chemotherapy would receive hormone therapy. As hormone therapy was not fully captured within the UK RWE, hormone therapy was added to the cost side of the basket of treatments for 20% of the basket. Alternative methods to capture hormone therapy were unsuccessful: No PFS and OS data for hormone therapy in patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy were found in the literature, only in the first line setting. Feedback from UK clinical experts strongly indicated that any data for patients not in the post-platinum chemotherapy setting would not be suitable to use as a proxy for these comparators.	exploring the efficacy of hormone therapy based on the published literature were conducted. The assumption that hormone therapy efficacy is equivalent to that of chemotherapy is conservative and optimistic for hormone therapy. The fact that this is a conservative assumption has been validated by UK clinical experts.
	Of patients receiving hormone therapy, 50% are assumed to receive medroxyprogesterone acetate and 50% are assumed to receive letrozole.	UK clinical expert opinion indicated that medroxyprogesterone acetate and letrozole are the two most commonly used hormone therapies in UK clinical practice in this setting. In the absence of more detailed prescribing data, it is assumed that equal numbers of patients receive either treatment.	A conservative scenario analysis has been conducted where all patients receiving hormone therapy receive letrozole, the cheaper of the two hormone therapies.
Subsequent treatments	Patients receiving dostarlimab are assumed to receive subsequent treatments in line with treatments received by ≥ 5% of 2L patients in the UK RWE study; patients receiving current clinical management are assumed to receive subsequent	UK clinical expert opinion validated that this assumption would be in line with the subsequent treatments that patients would be expected to receive in UK clinical practice following treatment with either dostarlimab or current clinical management.	A scenario analysis has been conducted where patients receiving dostarlimab receive subsequent treatments in line with subsequent treatments

	treatments in line with treatments received by ≥ 5% of 3L patients in the UK RWE study. In addition, based on UK clinical expert feedback, hormone therapy and radiotherapy were included as subsequent treatments in both arms of the base case cost-effectiveness analysis.		received in the GARNET trial. No further scenario analyses were conducted to explore the impact of including hormone therapy and radiotherapy as part of the subsequent therapies received within the model.
Drug administration	Oral therapies do not incur any administration costs.	Oral therapies are taken in the patient's own home without need for clinical supervision.	NA.
Diagnostic testing	All patients are assumed to receive dMMR/MSI-H testing via IHC based on DG42.	NICE diagnostics guidance DG42 recommends that all patients with EC should be tested to identify tumours with dMMR/MSI-H.[18] DG42 recommends that testing for dMMR/MSI-H tumours should consist of dMMR testing via immunohistochemistry (IHC), and UK clinical expert opinion and NHS England input sought by GSK agreed that this would be the preferred testing approach and that all patients eligible for treatment with dostarlimab would receive dMMR testing as a result of this guidance, and that provision would be made.	A scenario analysis has been conducted where 42% of patients receiving dostarlimab (the percentage of patients with recurrent EC) incur the cost of dMMR/MSI-H testing via IHC. This conservative scenario analysis considers the possibility that proportion of the patients entering the model with recurrent EC may have been initially diagnosed with EC prior to the publication of DG42 in 2020 and would therefore would not be eligible for dMMR/MSI-H testing per DG42.

Abbreviations: dMMR: DNA mismatch repair deficiency; DG: diagnostics guidance; EC: endometrial cancer; HC: immunohistochemistry; IV: intravenous; MSI-H: microsatellite instability-high; NA: not applicable; OS: overall survival; PFS: progression-free survival; RWE: real-world evidence; ToT: time on treatment; TTNT: time-to-next treatment.

B.3.7 Base case results

B.3.7.1 Base case incremental cost-effectiveness analysis results

As discussed in Section B.3.2.3, the base case economic analysis compares the clinical and cost-effectiveness of dostarlimab versus current clinical management, using data collected by GSK in a UK RWE study.

In the base case economic analysis versus current clinical management, dostarlimab (at list price) was associated with an ICER of £[redacted] per QALY gained. When adopting the PAS price for dostarlimab, the estimated ICER for dostarlimab versus current clinical management was £50,221 per QALY gained.

As discussed in Section B.2.11.5, patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or after platinum-based chemotherapy are at an end-of-life stage. Data from the UK RWE study show that patients treated with current clinical management had a median OS of [redacted] months (95% CI: [redacted], [redacted]), and results from the base case economic analysis suggest that dostarlimab provides an extension to life versus current clinical management of [redacted] discounted life years.

Taken together, the results of the base case economic analysis (when dostarlimab is provided with the confidential PAS) demonstrate that dostarlimab is a cost-effective treatment for patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or after platinum-based chemotherapy when considering the NICE willingness-to-pay threshold of £50,000 per QALY gained.

Table 78: Base case deterministic economic analysis results[a] (dostarlimab list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Current clinical management	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Discounted costs, LYs and QALYs.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life year.

Table 79: Base case deterministic economic analysis results[a] (dostarlimab PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Current clinical management	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,221

Footnotes: [a] Discounted costs, LYs and QALYs.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life

year; PAS: patient access scheme.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted in order to assess the impact of parameter uncertainty on the results of the cost-effectiveness analysis. The PSA was run for 10,000 iterations and in each iteration model inputs for all parameters were randomly drawn from specified distributions (e.g. gamma for costs, beta for proportions, and lognormal for HRs). Where possible the standard error or standard deviation associated with the mean value was used to define the distribution, otherwise it was assumed that the standard error would be 20% of the mean value. The inputs and distributions used in the PSA are summarised in Table 80.

Table 80: PSA inputs and distributions

Parameter	Mean	Standard error	Alpha	Beta	Distribution
Clinical parameters					
Mu (Dostarlimab OS Generalised Gamma)	[redacted]	-	NA	NA	**Covariance-variance matrix**
Sigma (Dostarlimab OS Generalised Gamma)	[redacted]	-	NA	NA	
Q (Dostarlimab OS Generalised Gamma)	[redacted]	-	NA	NA	
Mean log (Dostarlimab PFS Log Normal)	[redacted]	-	NA	NA	**Covariance-variance matrix**
SD log (Dostarlimab PFS Log Normal)	[redacted]	-	NA	NA	
logShape (Dostarlimab ToT Log Logistic)	[redacted]	-	NA	NA	**Covariance-variance matrix**
logScale (Dostarlimab ToT Log Logistic)	[redacted]	-	NA	NA	
logShape (Current Clinical Management OS Log Logistic)	[redacted]	-	NA	NA	**Covariance-variance matrix**
logShape (Current Clinical Management OS Log Logistic)	[redacted]	-	NA	NA	
logScale (Current Clinical Management PFS Log Logistic)	[redacted]	-	NA	NA	**Covariance-variance matrix**
logScale (Current Clinical Management PFS Log Logistic)	[redacted]	-	NA	NA	
Mu (Current Clinical Management ToT Generalised Gamma)	[redacted]	-	NA	NA	**Covariance-variance matrix**
Sigma (Current Clinical Management ToT Generalised Gamma)	[redacted]	-	NA	NA	

Q (Current Clinical Management ToT Generalised Gamma)	[redacted]	-	NA	NA	
Cost and resource use					
Drug administration cost - IV administration (simple)	241.06	24.11	100.00	2.41	Gamma
Drug administration cost - IV administration (complex)	306.90	30.69	100.00	3.07	Gamma
Drug administration cost – IV administration (subsequent)	332.13	33.21	100.00	3.32	Gamma
Unit cost – Outpatient visit (consultant oncologist) – first	267.65	26.77	100.00	2.68	Gamma
Unit cost – Outpatient visit (consultant oncologist) – follow-up	176.45	17.65	100.00	1.76	Gamma
Unit cost – Blood test (Full blood count)	2.79	0.28	100.00	0.03	Gamma
Unit cost – CT scan	97.15	9.72	100.00	0.97	Gamma
Unit cost – Specialist nurse	50.00	5.00	100.00	0.50	Gamma
Unit cost – GP visit	39.00	3.90	100.00	0.39	Gamma
Unit cost – Nurse visit	48.00	4.80	100.00	0.48	Gamma
Cost per cycle – dostarlimab (phase 1 – every 3 weeks) (with PAS)[a]	[redacted]	[redacted]	100.00	[redacted]	Gamma
Cost per cycle - dostarlimab (phase 2 - every 6 weeks) (with PAS)[a]	[redacted]	[redacted]	100.00	[redacted]	Gamma
Cost per cycle – current clinical management[a]	328.56	32.86	100.00	3.29	Gamma
Cost per cycle – paclitaxel (part of carboplatin plus paclitaxel) (as subsequent therapy)[a]	22.07	2.21	100.00	0.22	Gamma
Cost per cycle – PLD (as subsequent therapy)[a]	1,068.74	106.87	100.00	10.69	Gamma
Cost per cycle – paclitaxel monotherapy (as subsequent therapy)[a]	37.23	3.72	100.00	0.37	Gamma
Cost per cycle – carboplatin (as subsequent therapy)[a]	14.84	1.48	100.00	0.15	Gamma
Cost per cycle –carboplatin plus gemcitabine (as subsequent therapy)[a]	66.12	6.61	100.00	0.66	Gamma
Cost per cycle – hormone therapy (as subsequent therapy)[a]	21.12	2.11	100.00	0.21	Gamma
Cost per cycle – radiotherapy (as subsequent therapy)[a]	2,722.78	272.28	100.00	27.23	Gamma
AE cost: abdominal pain	375.46	37.55	100.00	3.75	Gamma
AE cost: allergic reactions	404.73	40.47	100.00	4.05	

AE cost: anaemia	485.28	48.53	100.00	4.85	Gamma
AE cost: fatigue	0.00	0.00	0.00	0.00	Gamma
AE cost: hand and foot syndrome	404.73	40.47	100.00	4.05	Gamma
AE cost: leukopenia	431.19	43.12	100.00	4.31	Gamma
AE cost: mucosal inflammation	391.93	39.19	100.00	3.92	Gamma
AE cost: nausea	447.58	44.76	100.00	4.48	Gamma
AE cost: neutropenia	431.19	43.12	100.00	4.31	Gamma
AE cost: sensory neuropathy	351.03	35.10	100.00	3.51	Gamma
AE cost: stomatitis	391.93	39.19	100.00	3.92	Gamma
AE cost: thrombocytopenia	655.62	65.56	100.00	6.56	Gamma
AE cost: vomiting	447.58	44.76	100.00	4.48	Gamma
Resource use: PFS on treatment – Outpatient visit (consultant oncologist) – first	1.00	0.10	100.00	0.01	Gamma
Resource use: PFS on treatment – Outpatient visit (consultant oncologist) – follow-up	1.00	0.10	100.00	0.01	Gamma
Resource use: PFS on treatment – Blood test (full blood count)	1.00	0.10	100.00	0.01	Gamma
Resource use: PFS on treatment – CT scan	0.30	0.03	100.00	0.00	Gamma
Resource use: PFS on treatment – Specialist nurse	1.00	0.10	100.00	0.01	Gamma
Resource use: PFS on treatment – GP visit	1.00	0.10	100.00	0.01	Gamma
Resource use: PFS on treatment – Nurse visit	0.30	0.03	100.00	0.00	Gamma
Resource use: PFS off treatment – Outpatient visit (consultant oncologist) – follow-up	0.30	0.03	100.00	0.00	Gamma
Resource use: PFS off treatment – Blood test (full blood count)	0.30	0.03	100.00	0.00	Gamma
Resource use: PFS off treatment – CT scan	0.30	0.03	100.00	0.00	Gamma
Resource use: PFS off treatment – Specialist nurse	1.00	0.10	100.00	0.01	Gamma
Resource use: PFS off treatment – GP visit	1.00	0.10	100.00	0.01	Gamma
Resource use: PFS off treatment – Nurse visit	0.30	0.03	100.00	0.00	Gamma
Resource use: PD – Outpatient visit (consultant oncologist) – follow-up	0.30	0.03	100.00	0.00	Gamma

Resource use: PD – Blood test (full blood count)	0.30	0.03	100.00	0.00	Gamma
Resource use: PD – CT scan	0.30	0.03	100.00	0.00	Gamma
Resource use: PD – Specialist nurse	1.00	0.10	100.00	0.01	Gamma
Resource use: PD – GP visit	1.00	0.10	100.00	0.01	Gamma
Resource use: PD – Nurse visit	0.30	0.03	100.00	0.00	Gamma
End-of-life cost (one-off)	8,104.88	810.49	100.00	81.05	Gamma
Utility values					
Patient baseline utility	[redacted]	[redacted]	NA	NA	Covariance-variance matrix
Time to death > 5 cycles	[redacted]	[redacted]	NA	NA	
Progressed	[redacted]	[redacted]	NA	NA	
Constant	[redacted]	[redacted]	NA	NA	
AE disutility: abdominal pain	−0.069	0.007	100.000	−0.001	Gamma
AE disutility: allergic reactions	−0.116	0.012	100.000	−0.001	Gamma
AE disutility: anaemia	−0.119	0.012	100.000	−0.001	Gamma
AE disutility: fatigue	−0.073	0.007	100.000	−0.001	Gamma
AE disutility: hand and foot syndrome	−0.116	0.012	100.000	−0.001	Gamma
AE disutility: leukopenia	−0.090	0.009	100.000	−0.001	Gamma
AE disutility: mucosal inflammation	−0.151	0.015	100.000	−0.002	Gamma
AE disutility: nausea	−0.045	0.005	100.000	0.000	Gamma
AE disutility: neutropenia	−0.090	0.009	100.000	−0.001	Gamma
AE disutility: sensory neuropathy	−0.116	0.012	100.000	−0.001	Gamma
AE disutility: stomatitis	−0.151	0.015	100.000	−0.002	Gamma
AE disutility: thrombocytopenia	−0.090	0.009	100.000	−0.001	Gamma
AE disutility: vomiting	−0.103	0.010	100.000	−0.001	Gamma

Footnote: [a] Cost per cycle of dostarlimab and the relevant comparators was included in the PSA in order to investigate uncertainty related to the treatment dosing regimens and relative dose intensities, and the possible resulting impact on the cost per cycle of each treatment.
Abbreviations: AE: adverse event; CT: computerised tomography; GP: general practitioner; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PLD: pegylated liposomal doxorubicin; ToT: time on treatment.

The results of the PSA with 10,000 iterations are presented in Table 81 (list price) and Table 82 (with PAS for dostarlimab). Dostarlimab was associated with an [redacted]% probability of being cost-effective versus current clinical management at list price, and a [redacted]% probability of being cost-effective at PAS price.

Table 81: Base case PSA results[a] (dostarlimab list price)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)

Current clinical management	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Discounted costs, LYs and QALYs.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life year; PAS: patient access scheme.

Table 82: Base case PSA results[a] (dostarlimab PAS price)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Current clinical management	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,363

Footnotes: [a] Discounted costs, LYs and QALYs.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life year; PAS: patient access scheme.

Scatter plots showing the incremental costs and QALYs for dostarlimab versus current clinical management across all iterations in the PSA are presented in Figure 56 (list price) and Figure 57 (with PAS for dostarlimab). Cost-effectiveness acceptability curves are presented in Figure 58 (list price) and Figure 59 (with PAS for dostarlimab).

Figure 56: Cost-effectiveness acceptability curve for dostarlimab versus current clinical management (dostarlimab list price)

Abbreviations: QALYs: quality-adjusted life years.

Figure 57: Cost-effectiveness acceptability curve for dostarlimab versus current clinical management (dostarlimab PAS price)

Abbreviations: QALYs: quality-adjusted life years; PAS: patient access scheme.

Figure 58: Cost-effectiveness plane for dostarlimab versus current clinical management (dostarlimab list price)

Figure 59: Cost-effectiveness plane for dostarlimab versus current clinical management (dostarlimab PAS price)

Abbreviations: PAS: patient access scheme.

B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted by varying the input for each parameter in the model by ±20% of their mean value, whilst keeping all other inputs the same. For certain parameters where standard errors of the mean were available, the lower and upper limits were defined by the 95% CI around the mean. The inputs used in the DSA are presented in Table 83.

Table 83: One-way DSA inputs

Parameter	Mean	Lower value	Upper value
Cost and resource use			
Drug administration cost - IV administration (simple)	241.06	216.95	265.16
Drug administration cost - IV administration (complex)	306.90	276.21	337.59
Drug administration cost – IV administration (subsequent)	332.13	298.92	365.34
Unit cost – Outpatient visit (consultant oncologist) – first	267.65	240.89	294.42
Unit cost – Outpatient visit (consultant oncologist) – follow-up	176.45	158.81	194.10
Unit cost – Blood test (Full blood count)	2.79	2.51	3.07
Unit cost – CT scan	97.15	87.44	106.87
Unit cost – Specialist nurse	50.00	45.00	55.00
Unit cost – GP visit	39.00	35.10	42.90
Unit cost – Nurse visit	48.00	43.20	52.80
Cost per cycle – dostarlimab (phase 1 - every 3 weeks) (with PAS)[a]	[redacted]	[redacted]	[redacted]
Cost per cycle – dostarlimab (phase 2 - every 6 weeks) (with PAS)[a]	[redacted]	[redacted]	[redacted]

Cost per cycle – current clinical management[a]	328.56	295.71	361.42
Cost per cycle – paclitaxel (part of carboplatin plus paclitaxel) (as subsequent therapy)[a]	22.07	19.86	24.28
Cost per cycle – PLD (as subsequent therapy)[a]	1,068.74	961.86	1,175.61
Cost per cycle – paclitaxel monotherapy (as subsequent therapy)[a]	37.23	33.51	40.95
Cost per cycle – carboplatin (as subsequent therapy)[a]	14.84	13.36	16.32
Cost per cycle – carboplatin plus gemcitabine (as subsequent therapy)[a]	66.12	59.50	72.73
Cost per cycle – hormone therapy (as subsequent therapy)[a]	21.12	19.01	23.23
Cost per cycle – radiotherapy (as subsequent therapy)[a]	2,722.78	2,450.50	2,995.06
AE cost: abdominal pain	375.46	337.91	413.00
AE cost: allergic reactions	404.73	364.25	445.20
AE cost: anaemia	485.28	436.75	533.81
AE cost: fatigue	0.00	0.00	0.00
AE cost: hand and foot syndrome	404.73	364.25	445.20
AE cost: leukopenia	431.19	388.08	474.31
AE cost: mucosal inflammation	391.93	352.74	431.13
AE cost: nausea	447.58	402.82	492.34
AE cost: neutropenia	431.19	388.08	474.31
AE cost: sensory neuropathy	351.03	315.92	386.13
AE cost: stomatitis	391.93	352.74	431.13
AE cost: thrombocytopenia	655.62	590.05	721.18
AE cost: vomiting	447.58	402.82	492.34
Resource use: PFS on treatment – Outpatient visit (consultant oncologist) – first	1.00	0.90	1.10
Resource use: PFS on treatment – Outpatient visit (consultant oncologist) – follow-up	1.00	0.90	1.10
Resource use: PFS on treatment – Blood test (full blood count)	1.00	0.90	1.10
Resource use: PFS on treatment – CT scan	0.30	0.27	0.33
Resource use: PFS on treatment – Specialist nurse	1.00	0.90	1.10
Resource use: PFS on treatment – GP visit	1.00	0.90	1.10
Resource use: PFS on treatment – Nurse visit	0.30	0.27	0.33
Resource use: PFS off treatment – Outpatient visit (consultant oncologist) – follow-up	0.30	0.27	0.33
Resource use: PFS off treatment – Blood test (full blood count)	0.30	0.27	0.33
Resource use: PFS off treatment – CT scan	0.30	0.27	0.33
Resource use: PFS off treatment – Specialist nurse	1.00	0.90	1.10
Resource use: PFS off treatment – GP visit	1.00	0.90	1.10

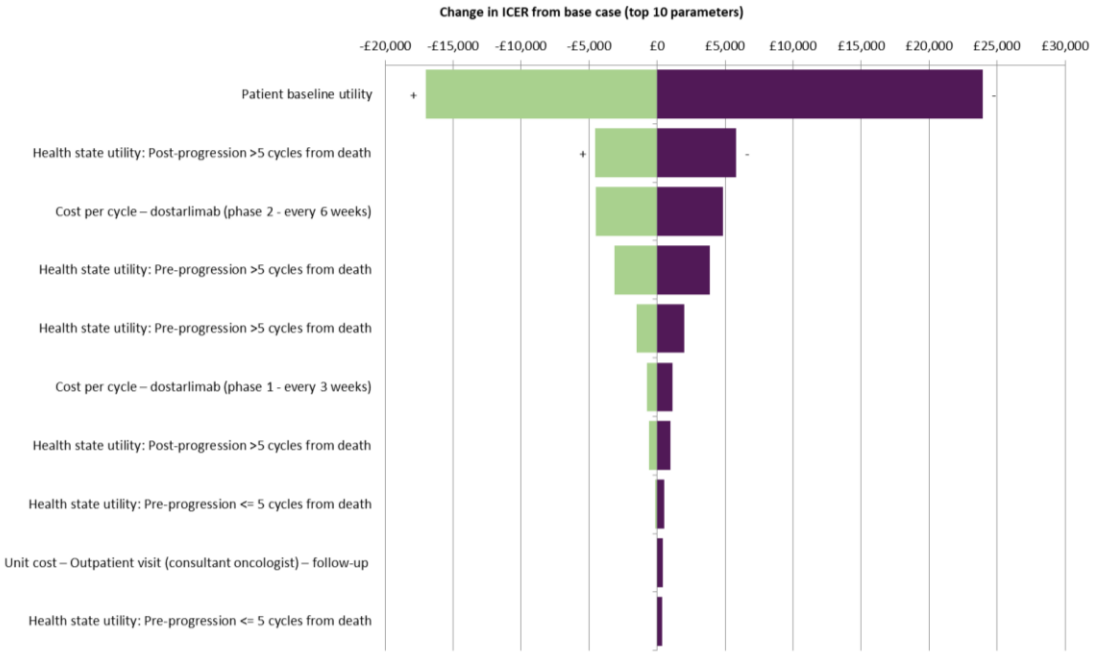
Resource use: PFS off treatment – Nurse visit	0.30	0.27	0.33
Resource use: PD – Outpatient visit (consultant oncologist) – follow-up	0.30	0.27	0.33
Resource use: PD – Blood test (full blood count)	0.30	0.27	0.33
Resource use: PD – CT scan	0.30	0.27	0.33
Resource use: PD – Specialist nurse	1.00	0.90	1.10
Resource use: PD – GP visit	1.00	0.90	1.10
Resource use: PD – Nurse visit	0.30	0.27	0.33
End-of-life cost (one-off)	8,104.88	7,294.40	8,915.37
Utility values			
Patient baseline utility	[redacted]	[redacted]	[redacted]
Health state utility value: Pre-progression >5 cycles from death	[redacted]	[redacted]	[redacted]
Health state utility value: Pre-progression ≤5 cycles from death	[redacted]	[redacted]	[redacted]
Health state utility value: Post-progression >5 cycles from death	[redacted]	[redacted]	[redacted]
Health state utility value: Post-progression ≤ 5 cycles from death	[redacted]	[redacted]	[redacted]
AE disutility values			
AE disutility: abdominal pain	−0.069	−0.062	−0.076
AE disutility: allergic reactions	−0.116	−0.104	−0.128
AE disutility: anaemia	−0.119	−0.107	−0.131
AE disutility: fatigue	−0.073	−0.066	−0.080
AE disutility: hand and foot syndrome	−0.116	−0.104	−0.128
AE disutility: leukopenia	−0.090	−0.081	−0.099
AE disutility: mucosal inflammation	−0.151	−0.136	−0.166
AE disutility: nausea	−0.045	−0.041	−0.050
AE disutility: neutropenia	−0.090	−0.081	−0.099
AE disutility: sensory neuropathy	−0.116	−0.104	−0.128
AE disutility: stomatitis	−0.151	−0.136	−0.166
AE disutility: thrombocytopenia	−0.090	−0.081	−0.099
AE disutility: vomiting	−0.103	−0.093	−0.113
AE disutility: investigation (white blood cell decreased)	0.000	0.000	0.000
AE disutility: investigation (neutrophil count decreased)	0.000	0.000	0.000

Footnote: [a] Cost per cycle of dostarlimab and the relevant comparators was included in the PSA in order to investigate uncertainty related to the treatment dosing regimens and relative dose intensities, and the possible resulting impact on the cost per cycle of each treatment.
Abbreviations: AE: adverse event; CT: computerised tomography; GP: general practitioner; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PLD: pegylated liposomal doxorubicin; ToT: time on treatment.

Tornado diagrams presenting the top 10 parameters with the greatest impact on the base case ICER for dostarlimab versus current clinical management are presented in Figure 60 (list price) and Figure 61 (with PAS for dostarlimab).

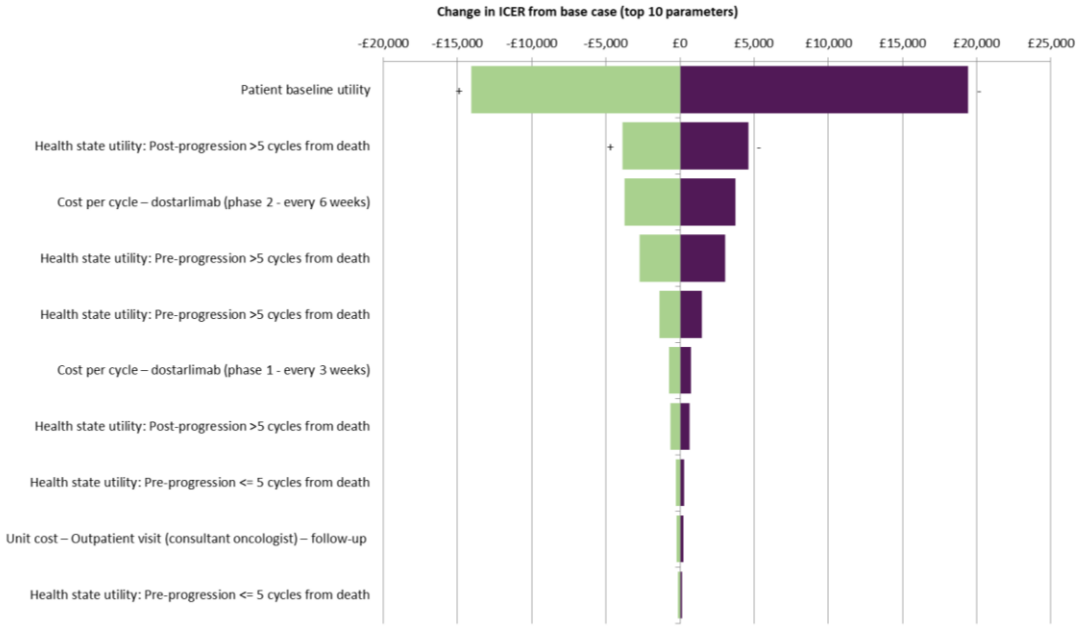
The parameters with the greatest impact on the base case ICER for dostarlimab versus current clinical management were the patient baseline utility values in GARNET, the pre- and post-progression health state utility values for patients >5 cycles from death and the cost per cycle of dostarlimab.

Figure 60: DSA tornado plot for dostarlimab versus current clinical management (dostarlimab list price)



Abbreviations: DSA: deterministic sensitivity analysis.

Figure 61: DSA tornado plot for dostarlimab versus current clinical management (dostarlimab PAS price)



Abbreviations: DSA: deterministic sensitivity analysis; PAS: patient access scheme.

B.3.8.3 Scenario analysis

43 scenario analyses were conducted to explore the impact of certain assumptions and alternative inputs within the base case economic analysis. Each scenario analysis is described in turn below, with full results of all scenario analyses presented in Table 85.

Current clinical management PFS (RWE outcome used as proxy)

As discussed in Section B.2.3.2 and Section B.2.11.3, the UK RWE study did not collect direct PFS data, because the NCRAS database does not include data collection for progression. Clinical expert opinion indicated that the use of TTNT, as per the base case as a PFS proxy, likely represents a conservative estimate because it is likely that patients would experience a delay between disease progression and start of next line of therapy. In order to explore the impact of this conservative assumption where TTNT is used as a PFS proxy, a scenario has been conducted where TTD from the UK RWE study is used as a proxy for PFS instead of TTNT.

- **Base case**: PFS for current clinical management is based on TTNT as a proxy for PFS
    - **Scenario 1:** PFS for current clinical management is based on TTNT as a proxy for PFS

Current clinical management PFS, OS and ToT (source population)

The base case cost-effectiveness analysis used efficacy data from the UK RWE GARNET-like cohort, which included patients with an ECOG PS or 0 and 1, as well as patients with an ECOG PS of 'unknown' (as previously detailed in Section B.2.3.2). In order to investigate the impact of including patients with an ECOG PS of 'unknown' a scenario analysis was conducted using the UK RWE GARNET-like ECOG PS ≤1 cohort, including only patients with an ECOG PS of 0 and 1, and excluding patients with an ECOG PS of 'unknown.'

- **Base case:** current clinical management PFS, OS and ToT data are derived from the UK RWE GARNET-like population
    - **Scenario 2:** current clinical management source of PFS, OS and ToT data are derived from the UK RWE GARNET-like ECOG PS ≤1 population (using the efficacy data for the ECOG PS ≤1 population presented in Appendix O.2, and the extrapolations detailed in Appendix P.4).

Current clinical management (extrapolations)

To explore the models used for the long-term extrapolation of PFS and OS in the base case cost-effectiveness analyses, a range of scenarios have been conducted using the best fitting alternative extrapolations considered to be clinically plausible (in line with the UK clinical expert estimates detailed in Section B.3.3.5 and B.3.3.6.).

- **Base case:** current clinical management PFS is extrapolated using the log-logistic model
    - **Scenario 3**: current clinical management PFS is extrapolated using the lognormal model
- **Base case:** current clinical management OS is extrapolated using the log-logistic extrapolation
    - **Scenario 4:** current clinical management OS is extrapolated using the generalised gamma model
    - **Scenario 5** : current clinical management OS is extrapolated using the lognormal model

Current clinical management (MAIC scenarios)

Two scenario analyses were conducted for current clinical management, exploring the application of the HRs from the UK RWE OS ITC to the dostarlimab OS extrapolation. Scenario 1 matched patients in the GARNET trial to those in the UK RWE study using the most important prognostic variables identified by clinical experts (excluding grade). Scenario 2 matched patients on prognostic variables as identified by regression analyses. A summary of the two scenarios can be found in Table 84, and further details on the prognostic matching can be found in Section B.2.7.1 and Appendix D.5.1.

Table 84: Scenarios considered in the UK RWE study MAICs versus GARNET

Scenarios	Prognostic variables
Scenario 1	• Histology[a] • Number of prior platinum-based therapies in the advanced/recurrent setting[b]
Scenario 2	• Race/ethnicity • Stage at diagnosis • Histology[a] • Prior surgery

Footnotes: [a] For scenarios including histology as a matching variable, one patient with an "unknown" histology was removed from the GARNET cohort in order to achieve balance. [b] For scenarios including the number of prior platinum-based therapies, patients with 0 or ≥2 prior platinum-based therapies from the GARNET cohort were removed in order to achieve balance.
Abbreviations: MAIC: matching-adjusted indirect comparison.

It is important to note that, given the fundamental difference in the mechanism of action of

dostarlimab, an I-O therapy, and individual chemotherapy regimens, the application of a HR is associated with substantial uncertainty. As described previously in Section B.1.3.6 and Section B.2.10, dostarlimab is a novel I-O therapy, which enables a patient's own immune system to mount an anti-tumour response. Successful treatment response following I-O therapies manifests differently compared to cytotoxic chemotherapy, and notably, may be associated with extended treatment benefits and long-term remission even after treatment discontinuation.[52, 65, 66] Such long-term treatment benefit is not typically associated with cytotoxic chemotherapy in this indication, as evidence by the UK RWE study, where just [redacted]% of patients receiving cytotoxic chemotherapy were alive after two years.

However, the application of a HR to the dostarlimab PFS and OS extrapolations, and the joint fitting of the curves, inherently assumes that the comparator chemotherapy will be associated with survival functions that display a similar shape and follow a similar trajectory to the dostarlimab survival functions, including the potential for long-term benefit and the extended tail of the KM curves that is the hallmark of I-O therapies.

Based on the published evidence of chemotherapy in EC (described in Appendix D.4.6), this is unlikely to be the case, and as such, the application of HRs to the dostarlimab extrapolations represents a key limitation of these analyses, and likely result in an overestimation of the long-term survival that would be associated with the chemotherapy regimens that constitute current clinical management.

- **Base case:** current clinical management OS is extrapolated using the log-logistic model, independently from OS in GARNET
    - **Scenario 6:** current clinical management OS extrapolation is based on the application of the HR from the UK RWE MAIC (Scenario 1; HR: [redacted]; 95% CI: [redacted], [redacted]) to the dostarlimab OS extrapolation
    - **Scenario 7:** current clinical management OS extrapolation is based on the application of the HR from the UK RWE MAIC (Scenario 2; HR: [redacted]; 95% CI: [redacted], [redacted]) to the dostarlimab OS extrapolation

Current clinical management (proportion of patients receiving hormone therapy)

Hormone therapy was not fully captured within the UK RWE study (Section B.2.7.3). As such, it was assumed that 20% of patients receiving current clinical management would incur the costs and AEs associated with hormone therapy, consisting of an equal proportion of patients receiving medroxyprogesterone acetate and letrozole, in line with UK clinical expert opinion. To explore any uncertainty associated with these assumptions, a number of alternative assumptions have been considered as scenario analyses, where varying proportions of patients incurred the costs and AEs associated with hormone therapy. The efficacy of current clinical management remained unchanged in each of the below scenarios.

- **Base case:** 20% of patients receiving current clinical management are assumed to receive hormone therapy
    - **Scenario 8:** 0% of patients receiving current clinical management are assumed to receive hormone therapy
    - **Scenario 9:** 10% of patients receiving current clinical management are assumed to receive hormone therapy

- **Scenario 10:** 30% of patients receiving current clinical management are assumed to receive hormone therapy

- **Base case:** 50% of patients receiving hormone therapy receive letrozole and 50% of patients receive medroxyprogesterone acetate
  - **Scenario 11:** 100% of patients receiving hormone therapy receive letrozole

Dostarlimab efficacy (extrapolations)

In order to explore the models used for long-term extrapolation of PFS and OS for patients treated with dostarlimab in the base case cost-effectiveness analyses, a range of scenarios have been conducted using the best fitting alternative extrapolations considered to be clinically plausible.

- **Base case:** dostarlimab PFS was extrapolated using the lognormal model
  - **Scenario 12:** dostarlimab PFS was extrapolated using the log-logistic model
  - **Scenario 13:** dostarlimab PFS was extrapolated using the generalised gamma model
- **Base case:** dostarlimab OS was extrapolated using the generalised gamma model (including treatment waning)
  - **Scenario 14:** dostarlimab OS was extrapolated using the lognormal model (excluding treatment waning)
  - **Scenario 15:** dostarlimab OS was extrapolated using the generalised gamma model (excluding treatment waning for OS; treatment waning is still applied to PFS)

Dostarlimab time on treatment (extrapolations and adjustments)

- **Base case:** Dostarlimab time on treatment was extrapolated using the log-logistic extrapolation, with [redacted]% of patients continuing on treatment at [redacted] with [redacted]% of patients discontinuing at [redacted])
  - **Scenario 16:** Dostarlimab time on treatment was extrapolated using the log-logistic extrapolation with [redacted]% of patients continuing on treatment at [redacted] with [redacted]% of patients discontinuing at [redacted]
  - **Scenario 17:** Dostarlimab time on treatment was extrapolated using the log-logistic extrapolation with [redacted]% of patients continuing on treatment at [redacted] with [redacted]% of patients discontinuing at [redacted]
  - **Scenario 18:** Dostarlimab time on treatment was extrapolated using the log-logistic extrapolation with [redacted]% of patients discontinuing treatment at [redacted]

Treatment waning scenarios (starting point and length of waning)

- **Base case:** Treatment waning for dostarlimab begun at [redacted] months, [redacted] after [redacted] patients discontinue treatment with dostarlimab, and was applied for [redacted] (i.e. waning was stopped [redacted] after initiation of treatment).
  - **Scenario 19:** Treatment waning for dostarlimab begun at [redacted] months, [redacted] after [redacted] patients discontinue treatment with dostarlimab, and was applied for [redacted] (i.e. waning was stopped [redacted] after initiation of treatment).

- **Scenario 20:** Treatment waning begun at [redacted] months, [redacted] after [redacted] patients discontinue treatment with dostarlimab, and was applied for [redacted] (i.e. waning was stopped [redacted] after initiation of treatment).
- **Scenario 21:** Treatment waning begun at [redacted] months, and was applied for [redacted] for PFS and [redacted] for OS (i.e. waning was stopped [redacted] and [redacted] after initiation of treatment for PFS and OS, respectively).

Utility values

- **Base case:** Utility values were derived from GARNET, and included time-to-death as a covariate and age-related utility adjustment.
  - **Scenario 22:** Pre-and post-progression utiliy values were derived from GARNET only ([redacted] and [redacted], respectively) (time-to-death was excluded as a covariate).
  - **Scenario 23:** Utility values were derived from GARNET, and included time-to-death as a covariate. Age-related utility adjustment was excluded.
- **Base case:** AE disutilities were included.
  - **Scenario 24:** AE disutilities were not included.

Diagnostic testing

- **Base case:** Diagnostic testing costs were not included.
  - **Scenario 25:** Diagnostic testing costs were included for all patients with recurrent EC (42%)

Subsequent therapies (source)

A scenario analysis was conducted where patients treated with dostarlimab receive subsequent treatments in line with those received by >1 patient in GARNET. Pembrolizumab was excluded as a subsequent treatment; it was received by [redacted] patients in GARNET as a subsequent treatment, however, it is only available privately in the UK, and therefore would not be included in routine subsequent treatment. The percentages of all other subsequent treatments in GARNET received by >1 patient were re-weighted accordingly. The re-weighted subsequent treatment distribution is presented in Appendix P.1.

- **Base case:** subsequent therapies for patients receiving dostarlimab were based on the distribution of subsequent therapies in the UK RWE study (mean subsequent treatment acquisition cost of £[redacted] across all cycles
  - **Scenario 26:** subsequent therapies for patients receiving dostarlimab were based on the distribution of subsequent therapies in GARNET (mean subsequent treatment acquisition cost of £[redacted] across all cycles (applied to patients receiving dostarlimab only, the subsequent treatment distribution is detailed in Appendix P.1)

Model structure

Various scenarios have been conducted to explore the impact on certain assumptions within the base case model structure. The following scenarios have been conducted:

- **Base case:** the model considered a time horizon of 40 years

    - **Scenario 27:** the model considered a time horizon of 20 years
    - **Scenario 28:** the model considered a time horizon of 30 years
- **Base case:** half-cycle correction was included
    - **Scenario 29:** half-cycle correction was not included
- **Base case:** the model considered a discount rate of 3.5% for both costs and outcomes
    - **Scenario 30:** the model considered a discount rate of 1.5% for costs and 3.5% for outcomes
    - **Scenario 31:** the model considered a discount rate of 6% for costs and 3.5% for outcomes
    - **Scenario 32:** the model considered a discount rate of 3.5% for costs and 1.5% for outcomes
    - **Scenario 33:** the model considered a discount rate of 3.5% for costs and 6% for outcomes
    - **Scenario 34:** the model considered a discount rate of 1.5% for both costs and outcomes

Pairwise comparisons versus individual chemotherapy regimens based on the published literature

As described previously in Section B.2.2 (Table 5), Section B.2.7.2 and Section B.2.11, given the distinct paucity of evidence identified for the individual comparator treatments in the literature, robust comparisons versus the individual comparator treatments listed within the NICE final scope were extremely difficult, and the use of the UK RWE study in the base case cost-effectiveness analysis was considered to be more robust.

Nevertheless, the ITCs conducted versus individual chemotherapy comparators based on the published literature, detailed in Section B.2.7.2, have been used to inform economic scenario analyses. For each of these scenarios, PFS and OS HRs were derived from the ITCs described in Section B.2.7.2 and were applied to the dostarlimab PFS and OS base case extrapolations to derive efficacy data for the individual chemotherapy comparator.

In addition to the limitations associated with the HR based approach detailed previously in this section with regard to the UK RWE MAIC scenarios, the limitations associated with the published literature and the resulting ITCs described in Section B.2.7.2 are important to consider. In particular, the comparisons using the results of the MAICs versus Makker *et al.* (2013), Julius *et al.* (2013), Rubinstein *et al.* (2019) and Mazgani *et al.* (2008) are associated with particular uncertainty.[7, 11, 59, 60] These were all retrospective, single-arm studies and associated with unknown levels of bias, given the paucity of reported patient characteristics and key prognostic variables meaning that the GARNET population could not be matched to the comparator studies with respect to multiple key prognostic variables. The small sample sizes of these studies, including 17, 41, 20 and 31 patients, respectively, represents a further limitation. These limitations, combined with the limitations of the HR based approach, means that the results of these MAICs, and any resulting scenarios must be interpreted with particular caution.

Scenarios which incorporate the results of the ITCs versus ZoptEC and McMeekin *et al.* (2015) represent more robust comparisons, as these were RCTs, which provided far more detailed data

on patient characteristics and key prognostic variables, while the ZoptEC IPD also allowed patients to be removed from both studies so that the cohorts could be closely matched.[6, 8-10] However, it was not possible to calculate a HR for PFS from either of these two comparisons, meaning that it was not possible to conduct economic scenarios using either of these two studies in isolation; any such scenarios required the use of PFS data from Makker *et al.* (2013), introducing the associated limitations.[11]

The scenarios using these ITCs are detailed in the following sections.

Comparisons versus doxorubicin monotherapy

Four studies included in the series of ITCs included doxorubicin monotherapy: ZoptEC, McMeekin *et al.* (2015) (in combination with paclitaxel), Makker *et al.* (2013) and Julius et al. (2015). [6, 7, 11] An OS HR was available versus each of these four studies, and therefore four scenarios were conducted, applying the OS HR from each study to the dostarlimab OS extrapolation. However, McMeekin *et al.* (2015) and Julius *et al.* (2013) did not report a PFS KM curve, while differences between the definition of PFS and the timepoints of tumour assessment in GARNET versus ZoptEC precluded the derivation of a PFS HR between the two studies. As such, it was necessary to apply the PFS HR from Makker *et al.* (2013) in all four scenarios.

The scenarios including a pairwise comparison versus doxorubicin monotherapy assume that the cost of doxorubicin monotherapy, and the AEs associated with doxorubicin monotherapy, are comprised of a weighted average of [redacted]% "naked" doxorubicin monotherapy and [redacted]% PLD, in line with the proportions of patients receiving each treatment in the UK RWE study. UK clinical expert opinion indicated that clinicians would typically only use PLD in UK clinical practice, meaning that that the inclusion of "naked doxorubicin" costs represents a conservative assumption which may underestimate the true costs associated with doxorubicin monotherapy in UK clinical practice.

The scenario analysis versus McMeekin *et al.* (2015) also assumes that doxorubicin and paclitaxel monotherapy are associated with equal efficacy as data are not presented individually for each treatment; clinical experts indicated that this is a reasonable assumption.

- **Base case:** Comparator efficacy source (base case: UK RWE study for current clinical management)
    - **Scenario 35:** Individual comparison versus doxorubicin monotherapy based on based on PFS from Makker *et al.* (2013)[11] (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]) and OS from the ZoptEC trial (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted])
    - **Scenario 36:** Individual comparison versus doxorubicin monotherapy based on PFS from Makker *et al.* (2013)[11] (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]) and OS from McMeekin *et al.* (2015)[6] (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted])
    - **Scenario 37:** Individual comparison versus doxorubicin monotherapy based on PFS (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]) and OS from Makker *et al.* (2013)[11] (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted])
    - **Scenario 38:** Individual comparison versus doxorubicin monotherapy using PFS from Makker *et al.* (2013)[11] (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]) and OS from Julius *et al.* (2013)[7] (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted])

Comparison versus paclitaxel monotherapy

The only relevant study in the published literature including data for paclitaxel monotherapy was McMeekin *et al.* (2015).[6]

A scenario was therefore conducted where the OS HR from McMeekin *et al.* (2015) was applied to the dostarlimab OS extrapolation. This assumes that doxorubicin and paclitaxel monotherapy are associated with equal efficacy as data are not presented individually for each treatment; as detailed previously in Section B.2.7.2, clinical experts indicated that this is a reasonable assumption.

McMeekin *et al.* (2015) treated patients with paclitaxel once every three weeks (Q3W), while clinicians indicated that patients with recurrent or advanced EC who had progressed on or after platinum-based chemotherapy would receive weekly paclitaxel in UK clinical practice. This scenario therefore assumes that paclitaxel Q3W and weekly paclitaxel are associated with equal efficacy – UK clinical experts indicated that on the basis of Rosenberg *et al.* (2002) and Homesley *et al.* (2008), this is a reasonable assumption.[121, 122]

As McMeekin *et al.* (2015) does not report a PFS KM curve, it is necessary to apply the PFS HR between dostarlimab and doxorubicin monotherapy in Makker *et al.* (2013), as detailed in in this section and Section B.2.7.2.

- **Base case:** comparative efficacy was modelled for current clinical management based on the UK RWE study
    - **Scenario 39:** an individual comparison versus paclitaxel monotherapy was conducted, based on PFS from Makker *et al.* (2013)[11] (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]) and OS from McMeekin *et al.* (2015)[6] (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted])

Comparisons versus carboplatin plus paclitaxel

Two scenarios were conducted versus carboplatin plus paclitaxel, applying PFS and OS HRs for dostarlimab from Rubinstein *et al.* (2019)[59] and Mazgani *et al.* (2008)[60], respectively. In addition to the substantial limitations associated with both of these scenarios noted previously, the scenario versus Rubinstein *et al.* (2019)[59] must be interpreted with further caution as the proportional hazards assumption was violated for both the PFS and OS MAICs (detailed in Appendix D.5.3), meaning that the use of a HR is not appropriate, however, given the small sample size of Rubinstein et al. (2019), there was no viable alternative.

- **Base case:** comparative efficacy was modelled for current clinical management based on the UK RWE study
    - **Scenario 40:** an individual comparison was conducted versus carboplatin plus paclitaxel using PFS (HR: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted]) and OS from Rubinstein *et al.* (2019)[59] (HR: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted])
    - **Scenario 41:** an individual comparison was conducted versus carboplatin plus paclitaxel using PFS (HR: [redacted], 95% CI: [redacted], [redacted]; p=[redacted]) and OS from Mazgani *et al.* (2008)[60] (HR: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted])

Comparisons versus carboplatin monotherapy

No evidence was identified for carboplatin monotherapy in the clinical SLR, and feedback from UK clinical experts strongly indicated that any data for patients not in the post-platinum

chemotherapy setting would not be suitable to use as a proxy for patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy. As such, it was not possible to conduct an individual comparison between dostarlimab and carboplatin monotherapy based on published literature for carboplatin monotherapy.

In order to investigate the cost-effectiveness of dostarlimab versus carboplatin, a scenario analysis was therefore conducted where the efficacy of carboplatin monotherapy was assumed to be equal to doxorubicin monotherapy. UK clinical experts indicated that this assumption was unlikely to be true, although, in the absence of any other viable alternatives, the assumption was considered to hold true for this scenario analysis.

- **Base case:** comparative efficacy was modelled for current clinical management based on the UK RWE study
    - **Scenario 42:** an individual comparison was conducted versus carboplatin monotherapy using doxorubicin monotherapy as a proxy for efficacy: based on PFS from Makker *et al.* (2013)[11] (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]) and OS from the ZoptEC trial (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted])

Pairwise comparison versus hormone therapy based on the UK RWE study

Similarly, despite efforts to identify published sources of evidence to use as a proxy for hormone therapy, feedback from UK clinical experts strongly indicated that any data for patients not in the post-platinum chemotherapy setting would not be suitable to use as a proxy for hormone therapy. As such, it was not possible to conduct an individual comparison between dostarlimab and hormone therapy based on the published literature available for hormone therapy.

As such, in order to investigate the cost-effectiveness of dostarlimab versus hormone therapy, a scenario was conducted where the efficacy of hormone therapy was assumed to be equal to current clinical management in the UK RWE study. This is a conservative assumption; UK clinical experts indicated that survival with hormone therapy would not be expected to exceed that observed in the UK RWE study. The UK clinical experts estimated that the median PFS and OS for hormone therapy in this setting would be ~ 3 months and ~ 6 months, respectively, whereas the median PFS for current clinical management from the UK RWE study was [redacted] months and the median OS was [redacted] months, respectively.

- **Base case:** comparative efficacy was modelled for current clinical management based on the UK RWE study, assuming that 20% of patients receiving current clinical management received hormone therapy
    - **Scenario 43:** an individual comparison was conducted versus hormone therapy. PFS, OS and ToT for hormone therapy assumed to be equal to the base case PFS and OS extrapolations for current clinical management

Table 85: Scenario analysis results[a]

No.	Description	List price			With PAS		
		Inc. costs	Incr. QALYs	ICER (£/QALY)	Inc. costs	Incr. QALYs	ICER (£/QALY)
	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,221
1	Current clinical management PFS = TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,366
2	Current clinical management based on ECOG PS ≤1 population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,155
3	Current clinical management PFS extrapolation = lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,184
4	Current clinical management OS extrapolation: generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,271
5	Current clinical management OS extrapolation: lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,765
6	Current clinical management OS extrapolation based on the application of the HR from the UK RWE MAIC (Scenario 1; HR: [redacted]) to the dostarlimab OS extrapolation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,249
7	Current clinical management OS extrapolation based on the application of the HR from the UK RWE MAIC (Scenario 2; HR: [redacted]) to the dostarlimab OS extrapolation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,917
8	Current clinical management proportion of patients receiving hormone therapy: 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,537
9	Current clinical management proportion of patients receiving hormone therapy: 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,878
10	Current clinical management proportion of patients receiving hormone therapy: 30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,565
11	Current clinical management proportion of patients receiving letrozole: 100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,232
12	Dostarlimab PFS extrapolation: Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,147

13	**Dostarlimab PFS extrapolation: Generalised gamma**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,252
14	**Dostarlimab OS extrapolation: Lognormal (excluding treatment waning)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,997
15	**Dostarlimab OS extrapolation: Generalised gamma (excluding treatment waning)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,677
16	**Time on treatment: loglogistic extrapolation with [redacted]% of patients continuing on treatment at [redacted] with [redacted]% of patients discontinuing at [redacted]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,804
17	**Time on treatment: loglogistic extrapolation with [redacted]% of patients continuing on treatment at [redacted] with [redacted]% of patients discontinuing at [redacted]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,439
18	**Time on treatment: loglogistic extrapolation with [redacted]% of patients discontinuing treatment at [redacted]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,847
19	**Treatment waning begins at [redacted], [redacted] after [redacted] discontinue treatment with dostarlimab, and is applied for [redacted]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,260
20	**Treatment waning begins at [redacted], [redacted] after [redacted] discontinue treatment with dostarlimab, and is applied for [redacted]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,633
21	**Treatment waning begins at [redacted], and is applied for [redacted] for PFS and [redacted] for OS**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,126
22	**Utility values: GARNET utility values (excluding time-to-death as a covariate)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,517
23	**Utility values: GARNET utility values (excluding age-related utility adjustment)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,911
24	**AE disutilities: not included**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,870
25	**Diagnostic testing costs: included for all recurrent patients (42%)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,261

26	**Subsequent therapies source: distribution of subsequent therapies based on those received in GARNET (applied to the GARNET arm only)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,251
27	**Time horizon: 20 years**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,393
28	**Time horizon: 30 years**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,492
29	**Half-cycle correction: not included**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,269
30	**Discount rate costs: 1.5%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,041
31	**Discount rate costs: 6%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,385
32	**Discount rate outcomes: 1.5%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,321
33	**Discount rate outcomes: 6%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,833
34	**Discount rate costs and outcomes: 1.5%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,891
35	**Individual comparison versus doxorubicin monotherapy based on based on PFS from Makker *et al.* (2013)[11] (HR: [redacted]) and OS from the ZoptEC trial (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£63,144
36	**Individual comparison versus doxorubicin monotherapy based on PFS from Makker *et al.* (2013)[11] (HR: [redacted];) and OS from McMeekin *et al.* (2015)[6] (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,284
37	**Individual comparison versus doxorubicin monotherapy based on PFS (HR: [redacted]) and OS from Makker *et al.* (2013)[11] (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,337
38	**Individual comparison versus doxorubicin monotherapy using PFS from Makker *et al.* (2013)[11] (HR: [redacted]) and OS from Julius *et al.* (2013)[7] (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,439
39	**Individual comparison versus paclitaxel monotherapy based on PFS from Makker *et al.* (2013)[11] (HR: [redacted]) and OS from McMeekin *et al.* (2015)[6] (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,911

40	**Individual comparison versus carboplatin plus paclitaxel using PFS (HR: [redacted]) and OS from Rubinstein *et al.* (2019)[59] (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
41	**Individual comparison versus carboplatin plus paclitaxel using PFS (HR: [redacted],) and OS from Mazgani *et al.* (2008)[60] (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£106,372
42	**Individual comparison versus carboplatin monotherapy using doxorubicin monotherapy as a proxy for efficacy: based on PFS from Makker *et al.* (2013)[11] (HR: [redacted]) and OS from the ZoptEC trial (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£65,367
43	**Current clinical management: proportion of patients receiving hormone therapy: 100%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,019

Footnotes: [a] Discounted costs, LYs and QALYs.
Abbreviations: AE: adverse events; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; MAIC: matched-adjusted indirect comparison; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; RWE: real-world evidence.

B.3.8.4 Summary of sensitivity analyses results

The PSA demonstrated that there is a [redacted]% probability of dostarlimab, at the with-PAS price, of being cost-effectiveness at a willingness-to-pay threshold of £50,000 per QALY gained.

Deterministic scenario analyses were conducted to explore uncertainty relating to both structural and parameter assumptions made in the base case cost-effectiveness analysis. In the scenario analyses, the results were largely stable when varying model assumptions, with the only scenarios to vary the ICER by more than £2,000 in either direction were those associated with the health state utility values from GARNET or the drug acquisition price of dostarlimab. Only one of the parameters varied changed the ICER by more than £5,000, demonstrating the robustness of the results.

The key scenario analyses showed dostarlimab represent a cost-effective treatment option across many of the key scenarios presented. Only a small minority (N=9) of the scenario analyses considered resulted in an increase of more than £5,000 to the ICER: the majority of these scenarios were based on pairwise comparisons versus the published literature, which, as described previously in Section B.2.2. B.2.7.2, B.2.11 and Section B.3.8.3, are associated with substantial uncertainty and limitations, and should be interpreted with caution.

B.3.9 Subgroup analysis

No economic subgroup analyses are relevant to this appraisal.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Technical validation

In alignment with best practice, validation of the economic model structure was conducted by an independent health economist expert, not previously involved in the model conceptualisation or programming.[123] Once fully developed, the model underwent two independent quality control and technical validation processes which included checking of all model calculations including standalone formulae, equations and Excel macros programmed in VBA. The correct functioning of the sensitivity and scenario analyses was also reviewed, and two checklists (for technical and stress test checks) were completed to ensure that the model generated accurate results which were consistent with input data and robust to extreme values.

Clinical validation

Extensive clinical validation was undertaken to validate the assumptions included within the base case cost-effectiveness analysis, as detailed throughout this section. Two full advisory boards were conducted with several clinical experts and these were followed by several one-to-one interviews with individual clinical experts.

The clinical experts provided feedback on almost all elements of the base case cost-effectiveness analysis, including validation of: the comparator choice, the extrapolations for PFS, OS and ToT, the treatment duration and treatment waning assumptions, the subsequent therapy assumptions, the AE rates and the dosing for comparator therapies, amongst others. As detailed

in B.3.3.5 and B.3.3.6, the base case PFS and OS extrapolations, in particular, were validated carefully with several clinical experts who provided estimates of landmark PFS and OS values over time in order for the most clinically plausible extrapolations to be chosen.

Comparison of model results with current clinical management

The results from the model for dostarlimab and current clinical management (UK RWE study) were compared to the equivalent results from the published studies to assess how closely they were aligned. The results presented in Table 86 and Table 87 clearly highlight that the model estimates for dostarlimab and current clinical management align reasonably well with the literature and a clear advantage for dostarlimab is observed versus current clinical management when comparing to both the published and modelled estimates.

Table 86: Comparison of PFS model results[a] with current clinical management

	PFS		
	Study median	Model median, months	Model mean, months
Dostarlimab (GARNET)	[redacted]	[redacted]	[redacted]
Current clinical management (UK RWE study)[13]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Undiscounted PFS estimates from the model are presented to aid comparison with the published literature.
Abbreviations: CI: confidence interval; PFS: progression free survival; RWE: real-world evidence; UK: United Kingdom.

Table 87: Comparison of OS model results[a] with current clinical management

	OS						
	Study median, months	Model median, months	Model mean, months	Study Pts alive at Month 24 (%)	Model Pts alive at Month 24 (%)	Study Pts alive at Month 60 (%)	Model Pts alive at Month 60 (%)
Dostarlimab (GARNET)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	[redacted]
Current clinical management (UK RWE study)[13]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Undiscounted PFS estimates from the model are presented to aid comparison with the published literature.
Abbreviations: CI: confidence interval; ITC: indirect treatment comparison; PLD: pegylated doxorubicin; OS: overall survival; RWE: real-world evidence; SLR: systematic literature review.

B.3.11 Interpretation and conclusions of economic evidence

Summary of the cost-effectiveness analysis

In the deterministic base case economic analysis, dostarlimab was associated with an additional [redacted] LYs and an additional [redacted] QALYs versus current clinical management. Including the

confidential PAS discount for dostarlimab, the base case ICER for dostarlimab versus current clinical management was £50,221 per QALY gained.

In the PSA, based on 10,000 iterations, the mean PSA results were similar to the deterministic base case results. Dostarlimab, when provided at the PAS price, was associated with an additional [redacted] LYs and an additional [redacted] QALYs versus current clinical management, and an ICER of £48,363 per QALY gained. The probability that dostarlimab (with PAS) is cost-effective at a £50,000 per QALY gained willingness-to-pay threshold is [redacted]. In the DSA, the parameters with the greatest effect on the base case ICER were patient baseline utility, pre- and post-progression health-state utility values for patients >5 cycles from death and the cost per cycle for dostarlimab.

Extensive scenario analyses were conducted to explore the impact of key model inputs and assumptions. The ICERs for dostarlimab (with PAS) were below the cost-effectiveness threshold of £50,000 per QALY gained across many of the key scenarios, demonstrating the robustness of the base case analysis.

These results demonstrate that dostarlimab would be a valuable and cost-effective addition to the treatment armamentarium for patients who would otherwise face an extremely poor prognosis due to lack of effective treatment options available to them.

Generalisability of the cost-effectiveness analysis

The economic evaluation is based on the patient population from the GARNET trial, which is considered representative of patients with recurrent or advanced EC. Furthermore, the efficacy for current clinical management was based on data from patients managed in real world clinical practice in the UK, making the analysis highly generalisable.

With the lack of definitive standard of care, a basket of comparator therapies including the most commonly prescribed chemotherapy regimens in UK clinical practice can be considered the most relevant comparator to dostarlimab. As per the NICE reference case, the analysis was conducted from an NHS and PSS perspective.

Strengths of the cost-effectiveness analysis

For the studies that were identified in the clinical SLR for comparator therapies, there was a distinct paucity of reported data. Given this limitation, and to provide a more accurate representation of the current clinical management, the UK RWE study was used to inform the efficacy for the comparator. This study included a population of patients closely aligned to the patients in GARNET that received a range of chemotherapy regimens that represent current clinical treatment paradigms in the UK.[13]

Other strengths of the evaluation are that the analysis meets all aspects of the NICE reference case, including performance of a cost-utility analysis from an NHS/PSS perspective, assessment of HRQoL using the EQ-5D, and discounting of costs and benefits at 3.5%. The analysis has similarly taken into account NICE's position statement regarding use of EQ-5D-5L data.[98]

Limitations of the cost-effectiveness analysis

The overarching limitation is the lack of head-to-head evidence between dostarlimab and the chemotherapy comparators. In order to overcome this limitation and inform the comparator in the model, the UK RWE study was conducted. Whilst generally the UK RWE study is a robust source

of evidence, it is subject to some limitations, including the underestimation of hormone therapy use compared to UK clinical practice, and the lack of dMMR status data (Section B.2.11).

Nevertheless, it is reasonable to assume that the base case cost-effectiveness analysis versus current clinical management, based on efficacy for chemotherapy regimens, is likely a conservative assumption. If hormone therapy had been fully captured in the UK RWE study, it is likely that the efficacy associated with current clinical management would have been reduced, as UK clinical experts indicated that the efficacy of hormone therapy would be substantially lower than chemotherapy for patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy (Section B.2.7.3).

Another limitation relates to the use of proxy measures for PFS and disease recurrence for the current clinical management comparator. This was necessary because the UK RWE study did not capture direct data for progression, remission or recurrence of disease. In light of this, TTNT was employed as a proxy for PFS in the base case cost-effectiveness analysis. UK clinical expert opinion indicated that this was a conservative assumption, given that TTNT would overestimate the PFS associated with current clinical management.

It was also not possible to conduct scenario analyses investigating the differences in PFS between the unadjusted and adjusted GARNET populations, as the inconsistencies between PFS in GARNET and TTNT in the UK RWE study precluded the derivation of a PFS HR between dostarlimab and current clinical management (unlike for OS where it was possible to investigate the use of HRs based on the RWE MAICs in scenario analyses). However, the adjusted GARBET population landmark PFS estimates at various timepoints were broadly similar to the unadjusted landmark estimates (Section B.2.7.1, Table 25), providing confidence that any differences between the GARNET and UK RWE GARNET-like populations would have only had a minimal impact on the true benefit for dostarlimab versus current clinical management.

Conclusion

Dostarlimab represents the only I-O monotherapy licensed for the treatment of patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or after platinum-based chemotherapy.[1] These patients currently face a dire prognosis, with extremely limited and inadequate treatment options based on unclear and inconsistent treatment guidelines. Data from the UK RWE study show that further chemotherapy in this setting is associated with an estimated median OS of just [redacted] months (95% CI: [redacted], [redacted]), with only [redacted]% and [redacted]% of patients alive after one and two years, respectively.[13]

The results of the base case cost-effectiveness analysis demonstrate dostarlimab to be a cost-effective use of NHS resources considering a willingness-to-pay threshold of ~£50,000 per QALY gained in this end-of-life condition. The results of the sensitivity and scenario analyses support the robustness of the base case analysis, and there was a [redacted]% chance of dostarlimab being cost-effective at this threshold (when provided at the PAS price).

For patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy, dostarlimab represents a step change in the clinical management of this condition and this analysis demonstrates that dostarlimab is a cost-effective use of NHS resources for these patients.

B.4 References

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B.5 Appendices

- Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: Subgroup analysis
- Appendix F: Adverse reactions
- Appendix G: Published cost-effectiveness studies
- Appendix H: Health-related quality-of-life studies
- Appendix I: Cost and healthcare resource identification, measurement and valuation
- Appendix J: Clinical outcomes and disaggregated results from the model
- Appendix K: Checklist of confidential information
- Appendix L: Targeted literature review – hormone therapy
- Appendix M: Targeted literature review – prognostic variables
- Appendix N: Additional information for the GARNET trial
- Appendix O: Additional information for the UK RWE study
- Appendix P: Cost-effectiveness model

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]

Clarification questions

June 2021

File name	Version	Contains confidential information	Date
[ID3802] dostarlimab - Clarification Letter ERG 2021-06-03 (AIC)	1	Yes	3 June 2021

Notes for company

Highlighting in the template

Square brackets and [redacted] highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [redacted] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Please present Document B Table 7 GARNET intention-to-treat (ITT) population baseline characteristics for the subgroups of (1) those with recurrent disease at baseline and (2) those with advanced disease at baseline. Please also present this for those attaining a best response of (1) complete response (CR), (2) partial response (PR) and (3) stable disease (SD). Please expand this data to include ECOG performance status at diagnosis if this data is available for GARNET.

[redacted]

A2. Please present Document B Table 13 real-world evidence (RWE) GARNET-like population characteristics for the subgroups of (1) those identified as having recurrent disease at GARNET equivalent baseline, (2) those with advanced disease at GARNET equivalent baseline, (3) those with endometrioid disease at diagnosis and identified as having recurrent disease at GARNET equivalent baseline and (4) those with endometrioid disease at diagnosis and with advanced disease at GARNET equivalent baseline. Please also present this for the RWE GARNET like Eastern Cooperative Oncology Group (ECOG) 0/1 population and the same four subgroups of it.

[redacted]

A3. Please provide the RWE GARNET-like population baseline characteristics equivalent to Document B Table 13 separately for people receiving carboplatin+paclitaxel (N=[redacted]), carboplatin+pegylated liposomal doxorubicin (PLD) (N=[redacted]), PLD monotherapy (N=[redacted]), paclitaxel monotherapy (N=[redacted]), carboplatin monotherapy (N=[redacted]) and cisplatin+doxorubicin (N=[redacted]).

[redacted]

A4. Please present a breakdown of the platinum doublets received by the RWE GARNET-like population prior to their second-line (2L) therapy in a similar format to company submission (CS) Document B Table 14.

[redacted]

A5. Document B Figure 9 only includes 35 people compared to the 47 people with an objective response rate (ORR) of Document B Table 16. Please provide an account of this. Please tabulate the data of Document B Figure 9 sufficient to reconstruct it, and if possible and appropriate expand this tabulation to the 47 people with an ORR of Document B Table 16. If the mean time to CR/PR could also be given this would be helpful, and if split by CR and PR even more so.

[redacted]

A6. PRIORITY Please provide the GARNET IA2 Kaplan Meier (KM) data in the same format as the following table of hypothetical data for overall survival (OS), progression-free survival (PFS) and time on treatment (ToT) for the ITT population (N=[redacted]), ITT endometrioid population (n=[redacted]) and OS, PFS, ORR and ToT for the Efficacy population (N=[redacted]) and Efficacy CR+PR population (N=[redacted]). Please present the same data restricted to the subgroups with (1) ECOG 0, (2) ECOG 1, (3) recurrent disease and ECOG 0 and (4) recurrent disease and ECOG 1.

Day	Month	Event	Censor	N at risk	S(t)
0	0.000	N=0	N=0	129	100%
3	0.099	N=0	N=2	127	100%
7	0.230	N=1	N=0	126	99%
10	0.329	N=4	N=2	120	96%
15	0.493	N=2	N=0	118	94%
etc...	etc...	etc...	etc...	etc...	etc...

[redacted]

A7. Please tabulate the GARNET IA2 reasons for OS events, OS censoring events, PFS events, PFS censoring events, ToT events, ToT censoring events and the number of people these apply to. Please provide this as disaggregate as possible, follow the classification of reasons of GARNET and do not follow the hypothetical reasons listed below. Where there may be ambiguity about the definition of a reason please provide a full description.

	OS		PFS		ToT	
Reason	Event	Censor	Event	Censor	Event	Censor
Death	N=???	n.a.	N=???	n.a.	N=???	N=???
Progression	N=???	N=???	N=???	n.a.	N=???	N=???
SAE	N=???	N=???	N=???	N=???	N=???	N=???
Study withdrawal	N=???	N=???	N=???	N=???	N=???	N=???
Etc…						

[redacted]

A8. PRIORITY Please provide the RWE GARNET-like KM data in the same format as the table of hypothetical data requested under A6 above for OS, time to next therapy (TTNT) and time to treatment discontinuation (TTD). As under A6, please present this separately for all populations, the four subgroups of A6 and the additional two subgroups of (5) ECOG undefined, (6) ECOG undefined recurrent. Please also present this restricted to all people with endometrioid disease and the six subgroups.

[redacted]

A9. Please provide the raw unmatched RWE GARNET-like KM data in the same format as the table of hypothetical data requested under A6 above for OS, TTNT and TTD separately for people receiving carboplatin+paclitaxel (N=[redacted]), carboplatin+PLD (N=[redacted]), PLD monotherapy (N=[redacted]), paclitaxel monotherapy (N=[redacted]), carboplatin monotherapy (N=[redacted]) and cisplatin+doxorubicin (N=[redacted]). The four subgroups of A6 are not required.

[redacted]

A10. PRIORITY Please provide two additional matching-adjusted indirect comparison (MAIC) analyses for the GARNET ITT endometrioid population with: (1) RWE GARNET-like population restricted to those with endometrioid disease; and, (2) RWE GARNET-like ECOG 0/1 population restricted to those with endometrioid disease. For each of these analyses please provide the resulting KM OS and PFS data for each arm in the same format as that requested under A6 above. NICE and the ERG realise that if this has not already been undertaken there will need to be flexibility on the timing of the provision of this.

[redacted]

A11. Please tabulate the KM data of Document B figures 23, 24, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37 separately by arm, excluding the unadjusted GARNET arm KM data already requested in other clarification questions, in the same format as that requested under A6 above. Please also supply this data equivalent to Document B figures 23, 24, 26, 27 for the MAIC of GARNET with the RWE GARNET-like ECOG 0/1 population.

[redacted]

A12. PRIORITY

a) **Please confirm that the Document B Figure 16 W3 to W96 are for people in PFS. Please confirm that end-of-treatment (EOT) to survival follow-up 5 (SUVF5) are for people who have finished treatment. Please define SFU and SUVF1 to SUVF5 in terms of weeks since EoT, to the extent possible. Please clarify if all people contributing to EoT and subsequent quality of life (QoL) assessments have necessarily progressed or have only necessarily ceased treatment.**

b) **For Document B Figure 16 please tabulate the values of each point and its 95% confidence interval and also tabulate the equivalent values for the ITT population, and also tabulate their equivalents for the EQ-5D-5L cross walked to the UK social tariff. Please also tabulate the GARNET EQ-5D-5L cross walked to the UK social tariff in the following format,**

separately for (1) the ITT population, (2) the Efficacy population and (3) the ITT advanced at baseline population.

	Number of people		Mean QoL	
Timepoint	Eligible	Reporting	Baseline	Timepoint
Baseline	N=?	N=?	μ=?	μ=?
W3	N=?	N=?	μ=?	μ=?
W9	N=?	N=?	μ=?	μ=?
etc…	N=?	N=?	μ=?	μ=?
W96	N=?	N=?	μ=?	μ=?
EOT	N=?	N=?	μ=?	μ=?
SUV	N=?	N=?	μ=?	μ=?
SUVF1	N=?	N=?	μ=?	μ=?
etc…	N=?	N=?	μ=?	μ=?
SUVF5	N=?	N=?	μ=?	μ=?

[redacted]

A13. PRIORITY Regarding MAICs, please present the original full regression models used and results, including p-values and each of the backward elimination steps required to arrive at the final models applied to estimate each of the MAIC-adjusted KM curves. Please present these for both (1) the GARNET vs RWE GARNET-like MAIC, and (2) the GARNET vs RWE GARNET-like ECOG 0/1 MAIC.

[redacted]

A14. Please provide the number and baseline characteristics of people receiving hormone therapy as second-line treatment in advanced or recurrent setting in the UK RWE GARNET-like population, had they not been excluded (The ERG is aware that use of hormone therapy was incompletely captured).

[redacted]

A15. Number of prior lines of therapy, CS Document B Table 7. Please confirm if lines of treatment have the same definition in GARNET and UK RWE. Please confirm if the lines of treatment noted refer to those received in recurrent and advanced setting or in pre-recurrent and advanced setting. Please confirm if all prior therapies for the GARNET population are platinum-based therapies. Please confirm

if platinum-based therapy is the last line of therapy prior to dostarlimab for all GARNET participants.

[redacted]

A16. Definition of recurrence – Please confirm if UK RWE recurrent population had some sort of radiographic evidence to confirm recurrence; and recurrence definition did not rely on only 90 days interval between treatments. UK RWE study Document B Page 49 - Table 10 Footnotes – “patients who were FIGO Stage I/II and received surgery, systemic anti-cancer therapy or radiation therapy and then had a treatment gap greater than 90 days, followed by treatment with any treatment”.

[redacted]

A17. Please provide information on baseline characteristics in ZoptEC (ITT population; N=255) in the same format as Appendix Page 111 - Table 40: Comparison of baseline characteristics in ZoptEC and GARNET.

[redacted]

A18. Please provide more information on the rationale for excluding people with follow-up greater than 36 months in the ZoptEC study (Appendices Page 116, Table 44:). Please provide the rationale for not using the same exclusion criteria for RWE GARNET-like population.

[redacted]

A19. Appendices Table 31 regression output: the title indicated n=[redacted] (as would be expected for RWE GARNET-like population), but data in the table suggest that only 926 people were included in the analysis. Please clarify.

[redacted]

A20. Please provide information on time since initial diagnosis at trial baseline for GARNET ITT and ZoptEC populations and the equivalent data for GARNET-like RWE population.

[redacted]

A21. Please provide information on the median duration of follow-up for GARNET ITT population at IA2.

[redacted]

Section B: Clarification on cost-effectiveness data

B1. PRIORITY For Tables 51, 53, 56, 58 and 62 clarify the uncertainty/range around each table cell. Please clarify the method of eliciting these values and all data that was communicated to the experts prior to them providing their opinions; e.g. GARNET OS KM S(t), OS KM S(t) 95% confidence limits, GARNET OS KM N at risk, RWE OS KM S(t), OS KM S(t) 95% confidence limits, RWE OS KM N at risk etc. prior to them making their estimates. If possible, please provide copies of the background briefing and questionnaire, together with an outline of how the elicitation exercise was conducted; e.g. online questionnaire, individual telephone interviews, group meeting.

[redacted]

B2. PRIORITY

a) **Please provide a full account of the GARNET QoL statistical analyses together with copies of any relevant internal GSK report(s) relating to this, including but not limited to method, population group baseline characteristics (N=[redacted]), N observations through time, models explored, coefficients, s.e. and p values, goodness of fit with the goodness of fit measures expanded to include some that take into account of the number of explanatory variables; e.g. $R^{-}\hat{}2$, AIC, etc..**

b) **Please outline why pseudonymised personal identifiers were used rather than actual personal identifiers given that Figure 16 makes no mention of this, and how the pseudonymised personal identifiers were arrived at.**

c) **Please provide a statistical justification for the model chosen for the base case. Please provide any additional analyses that were undertaken**

and also further analyses that explore additional variables including combinations of (1) varying the 5 cycles to death to 1 cycle (7 days), 3 cycles, 7 cycles and 9 cycles to death identifying which appears to be the best statistically, (2) ECOG 0 at baseline and (3) recurrent disease at baseline, reporting coefficients, s.e. and p values, goodness of fit etc..

d) **Please provide the arithmetic that causes the values of Appendix D Tables 157 and 158 to lead to the values of Document B Table 64.**

[redacted]

B3. PRIORITY

a) **Please provide more detail of the elicitation method for the [redacted] proportion of Table 62 together with any GSK data on file report relating to this, outline the questions posed, the individual responses received and ranges around these individual responses and whether the elicited responses specified a two-year time point or if this was prespecified during the elicitation exercise.**

b) **Please clarify whether the experts were briefed with the GARNET ToT KM data and the base case fitted curve prior to them responding and whether the implication that their responses would result in something akin to Figure 54 was communicated to them. Please also clarify whether the experts suggested that an absolute [redacted] would remain on treatment from year 2 onwards or whether 1-[redacted] of people remaining on treatment at 2 years would discontinue treatment.**

c) **If possible, please provide copies of the background briefing and questionnaire, together with an outline of how the elicitation exercise was conducted; e.g. online questionnaire, individual telephone interviews, group meeting.**

d) **Please outline any clinical rationale(s) given by the experts that among people in PFS and tolerant of dostarlimab (1) [redacted] would remain on treatment at 2 years and (2) all people would cease treatment at 5 years. Please outline the overarching company clinical rationale, i.e. without**

reference to previous assessments, for these two points in the light of the SmPC.

e) **Has the company elicited any patient/carer involvement around treatment cessation assumptions?**

[redacted]

B4. It is difficult to align the number of people reported in Table 31 with the GARNET ToT KM values reported in the electronic model ToT worksheet cells AI10:AI54. Please provide an account of how these values are aligned with one another.

[redacted]

B5. PRIORITY Please confirm that the RWE number of subsequent chemotherapy regimens of Document B 2nd paragraph page 135 was the number of people receiving at least one additional chemotherapy regime subsequent to their 2L chemotherapy regime. Please also provide the equivalent numerator and denominator restricted to those with an Endometrioid diagnosis. Please state the total number of people in GARNET who had received a subsequent treatment at IA2 and the total number of subsequent treatments received at IA2.

[redacted]

B6. The economic model reports a log hazard ratio (HR) for doxorubicin of [redacted] which would appear to imply an HR of [redacted], but an HR of [redacted] is reported. Please provide an account of this.

[redacted]

B7. Please tabulate the electronic model settings, with full cell referencing, that are required to generate each of the scenarios of Document B Table 85.

[redacted]

B8. Document B Page 137 states: “Additionally, in order to ensure that any OS extrapolations did not provide implausible estimates of mortality, all mortality rates used in the model were bound by the age- and gender-specific natural mortality of the general population as a minimum (calculated using England and Wales life

tables [2017–2019]). Adjustments were made in the model traces to ensure that logical inconsistencies, such as the proportion of people alive being less than the proportion of people alive and progression-free, could not occur (i.e. PFS was bound by OS as a minimum)."

Please specify which of these potential adjustments apply in their base case and which do not apply.

[redacted]

B9. Document B, Section 3.3.7: quote clinicians' opinion on time remaining on dostarlimab treatment: is this a mean of several clinicians' opinions, how many were asked (was it the same six as in the predictions on OS and PFS). It is not clear how this was arrived at and there was no mention of uncertainty around the estimate. Please clarify.

[redacted]

Section C: Textual clarification and additional points

Reference pack

NICE and the ERG are aware that the company stated some of the items listed below are "not included within the reference pack as these are either GSK Data on File or not able to be shared", but wish to request the company to consider sharing them given their importance for the interpretation of findings presented in the company submission.

C1. Please provide the report for the recent advisory board of UK clinicians referred to in the 1st paragraph of B.1.3.6.1, together with any associated background briefing and questionnaire.

[redacted]

C2. Please provide copies of the data on file references 13, 16, and 54. If the GSK data on file referenced by Document B Tables 53, 56, 58 and 62 is not among these references, please provide this GSK data on file.

[redacted]

C3. There are three or more unpublished ‘data on file’ documents cited in CS Document B or CS Appendices that cannot be identified in the ‘reference pack’ folders supplied. Please provide all documents referred to (full, unredacted versions):

- CS Doc B reference number 16. [GSK Data on File]. 2021. Clinical Expert Feedback. Cited on pp 25, 133-134, 141.

- CS Appendices reference number 6. [GSK Data on File]. 2021. Cited in many places, including on pp 38, 40, 53, 56, 58, 123-125, 146-152, 154-155, 285, 288-292, 294. Text on page 123 refers to different time-points using this same reference number "…and Tables, Listings and Figures (TLFs) from July 2019,6 December 2019 (first data-cut),6 and March 2020 (second data-cut),6 provided by GSK" and CS Appendices Tables 13, 15 and 52 include references to 5, 6, 10-13a with a footnote for a that says "a Three GSK Data on File Tables, Listings and Figures documents were available and included within the SLR.".

- CS Appendices page 118 says "The programming language for the ZoptEC ITC is provided in the reference pack: ‘GSK Data on File (ZoptEC ITC code)’".

[redacted]

C4. Please provide the final Statistical Analysis Plan (SAP) for the GARNET study.

[redacted]

Literature search and study selection

C5. DARE and HTA database are listed in the Information sources in CS Appendices, section D.2, but only CDSR/CENTRAL are mentioned in the top row of tables 6 and 7 and in table 12. Please clarify whether or not these databases were searched and provide numbers for each source.

[redacted]

C6. The bibliographic databases Science Citation index (Web of Science) and Conference proceedings Citation Index-Science (CPCI-S) (Web of Science) are listed in information sources in CS Appendices, section D.2, but we don't have search strategies for them. PharmNet.Bund and WHO ICTRP are also listed, but the search strategies and numbers are not provided. Please clarify whether or not these sources were searched and provide full search strategies with search date, search terms, and numbers for each source.

[redacted]

C7. The introduction to the targeted literature review (TLR) for clinical evidence on the efficacy and safety of hormone therapy (Appendix L) reports that Pubmed Central (a full text database) was searched, but later (under 'L.4 Search results'), the much larger database Pubmed is mentioned. Please clarify whether Pubmed Central or Pubmed were searched for the TLR.

[redacted]

C8. Cost-effectiveness: please provide a table of excluded references, with full citations and reasons, for the 20 records screened at full-text and excluded in the economic TLR update.

[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]

Clarification questions

June 2021

File name	Version	Contains confidential information	Date
[ID3802] dostarlimab - Clarification Letter ERG 2021-06-03 (AIC)	1	Yes	3 June 2021

Notes for company

Highlighting in the template

Square brackets and [redacted] highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [redacted] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Please present Document B Table 7 GARNET intention-to-treat (ITT) population baseline characteristics for the subgroups of (1) those with recurrent disease at baseline and (2) those with advanced disease at baseline. Please also present this for those attaining a best response of (1) complete response (CR), (2) partial response (PR) and (3) stable disease (SD). Please expand this data to include ECOG performance status at diagnosis if this data is available for GARNET.

Following the clarification call with the ERG and NICE on Friday 18th June, GSK understand that the additional baseline characteristics listed above have been requested to reduce uncertainty in the comparability of the GARNET and UK RWE study data.

Following the call, GSK endeavoured to obtain the baseline characteristics for patients with advanced disease and for patients with recurrent disease. Unfortunately, specific identifiers to separate these groups at baseline are not available in the GARNET data. This is due to how this criterion was recorded – the inclusion criterion was recorded combined: 'patient with proven recurrent or advanced solid tumour and has disease progression after treatment with available anti-cancer therapies'. It was not recorded separately for patients with recurrent versus advanced disease. As a result, it is not possible to obtain any data specific to these subgroups. Additionally, unfortunately ECOG performance status (PS) at diagnosis data are also not available from GARNET. Consequently, it is not possible to submit these data in response to this question.

Nevertheless, it is important to consider that the GARNET A1 cohort is itself a biomarker-specific subpopulation. GSK believe that providing data for multiple additional, smaller

subgroups is not relevant given additional subgroups were not defined in the NICE final scope for this appraisal. Furthermore, the GARNET A1 cohort was not statistically powered to draw meaningful conclusions for any further subgroups. Engagement with clinical experts identified the significant unmet need in endometrial cancer (EC) that exists across all patients who are included in the licensed indication for dostarlimab. These experts are clear that having a licensed treatment option for women with DNA mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) EC represents a significant step change in the clinical management for these patients. This is consistent with the temporary off-label availability of nivolumab monotherapy via the Cancer Drugs Fund (CDF) through a COVID-19 response programme for all patients with dMMR/MSI-H EC. In fact, at a recent meeting with clinical experts, it was suggested that histology may not feature in future clinical guidelines for EC, but that molecular subtyping identified via predictive biomarker testing will guide treatment and management options. Given that NICE DG42 has recommended biomarker testing to people who are newly diagnosed with EC, and dMMR/MSI-H serves as a predictive biomarker for immuno-oncology treatment response, the GARNET ITT population represents a clinically relevant subpopulation of EC, for which the trial was statistically powered to evaluate.

Separately to the above discussion, GSK note that CR, PR and SD are post-baseline events, meaning that they occur at timepoints after patients were enrolled into the trial and their baseline characteristics were recorded. As such, the baseline characteristics for patients that attained these outcomes would not be statistically meaningful to present.

A2. Please present Document B Table 13 real-world evidence (RWE) GARNET-like population characteristics for the subgroups of (1) those identified as having recurrent disease at GARNET equivalent baseline, (2) those with advanced disease at GARNET equivalent baseline, (3) those with endometrioid disease at diagnosis and identified as having recurrent disease at GARNET equivalent baseline and (4) those with endometrioid disease at diagnosis and with advanced disease at GARNET equivalent baseline. Please also present this for the RWE GARNET like Eastern Cooperative Oncology Group (ECOG) 0/1 population and the same four subgroups of it.

As highlighted in response to Question A1, GSK understand that the additional baseline characteristics listed above have been requested to reduce uncertainty in the comparability of the GARNET and UK RWE study data.

GSK believe that significant effort has already been taken to provide a robust external comparator arm to dostarlimab in the form of the National Cancer Registry Analysis System (NCRAS) UK RWE study. This study was designed to capture GARNET-like patients as closely as possible, and a naïve comparison of the UK RWE study and GARNET baseline characteristics showed similarity across almost all the characteristics considered (Table 15, Document B).

In order to minimise any uncertainty associated with any differences in ECOG PS, the

biggest difference between the two populations, a sensitivity analysis was conducted to compare outcomes between the base case GARNET-like UK RWE study population, which included patients with an ECOG PS of 'not recorded (NR)', and the GARNET-like ECOG PS ≤1 cohort which included only patients with a known ECOG PS of 0 or 1. Only minor differences were observed between the progression-free survival (PFS) and overall survival (OS) outcomes for the two populations, demonstrating that the inclusion of patients with an ECOG PS of 'NR' does not impact the comparability of the GARNET-like UK RWE study population with patients in the GARNET trial.

Furthermore, the comparability of the GARNET-like UK RWE study cohort to patients in the GARNET trial was supported by the results of the matching-adjusted indirect comparison (MAIC) between the two studies which was conducted in line with NICE DSU 18.[1] Minor differences between the unadjusted and adjusted OS hazard ratios (HRs) suggest that the two populations were closely matched, with only minimal differences with respect to key prognostic variables. The results also suggested that any remaining differences may actually lead to an underestimation of the true PFS and OS benefit that dostarlimab may provide relative to current clinical management.

Considering the above, the company believe the GARNET ITT population and UK RWE study GARNET-like cohort (n=[redacted]) are sufficiently similar to provide a valid comparison for decision making within the decision problem for this appraisal.

However, in order to help the ERG better characterise the RWE population, GSK has endeavoured to obtain the requested data, but as described above, was not able to obtain recurrent and advanced populations from GARNET as this level of detail was not captured separately. Following the meeting with the ERG and NICE, GSK has been able to obtain baseline characteristics for patients with endometrioid disease at diagnosis. Baseline characteristics for the GARNET ITT population, the UK RWE GARNET-like population and the UK RWE GARNET-like ECOG PS ≤1, as well as patients with endometrioid disease in each of those populations, are presented in Table 1 below.

Nevertheless, it is important to reiterate the response provided to Question A1; further subgroup analyses of the licensed dostarlimab indication were not included in the NICE final scope and should not be considered relevant to this appraisal.

Table 1: Baseline characteristics for patients in GARNET and the UK RWE GARNET-like cohort (and ECOG PS ≤1 cohort), and stratified by endometrioid histology both each cohort

	GARNET		UK RWE GARNET-like cohort		UK RWE GARNET-like ECOG PS ≤1 cohort	
	GARNET ITT population (N=129)	GARNET patients with endometrioid disease (N=[redacted])	UK RWE GARNET-like cohort (N=[redacted])	UK RWE GARNET-like cohort with endometrioid disease (N=[redacted])	UK RWE GARNET-like ECOG PS ≤1 cohort (N=[redacted])	UK RWE GARNET-like ECOG PS ≤1 cohort with endometrioid disease (N=[redacted])
Age						
Mean age, years (STD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median age, years (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group						
<65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most recent ECOG PS at registry diagnosis (UK RWE study) or study entry (GARNET), n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most recent FIGO stage, n (%)[a]						
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes:[a] FIGO stage at baseline for GARNET; FIGO stage at registry diagnosis for the UK RWE study.

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynaecology and Obstetrics; ITT: intention-to-treat; RWE: real-world evidence; STD: standard deviation ; UK: United Kingdom.

A3. Please provide the RWE GARNET-like population baseline characteristics equivalent to Document B Table 13 separately for people receiving carboplatin+paclitaxel (N=[redacted]), carboplatin+pegylated liposomal doxorubicin (PLD) (N=[redacted]), PLD monotherapy (N=[redacted]), paclitaxel monotherapy (N=[redacted]), carboplatin monotherapy (N=[redacted]) and cisplatin+doxorubicin (N=[redacted]).

Baseline characteristics for patients in the UK RWE study GARNET-like cohort separated by chemotherapy regimen are presented in Table 2.

Data have only been provided for treatments which were prescribed to ≥5% of patients in the UK RWE study GARNET-like population. This includes carboplatin plus PLD, which is not in the NICE final scope, but nonetheless, given that it is prescribed to a substantial proportion of the RWE population, is included here for completeness. Cisplatin plus doxorubicin was prescribed to <5% of these patients, and was not listed in the NICE final scope as a relevant comparator, therefore baseline characteristics and survival outcomes for patients receiving cisplatin plus doxorubicin alone are not presented.

Table 2: Baseline characteristics for patients in the UK RWE study GARNET-like cohort by chemotherapy regimen

Characteristic	Carboplatin plus paclitaxel (N=[redacted])	Carboplatin plus PLD (N=[redacted])	PLD monotherapy (N=[redacted])	Paclitaxel monotherapy (N=[redacted])	Carboplatin monotherapy (N=[redacted])
Mean age, years (STD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median age, years (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group, n (%)					
<65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
65 to <75 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)					
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS at the time of registry diagnosis, n (%)[c]					
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Not recorded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology at diagnosis, n (%)					
Carcinosarcoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clear cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dedifferentiated/Undifferentiated carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endometrioid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mesonephroma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mucinous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neuroendocrine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-specific	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-specific carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sarcoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIGO stage at the time of registry diagnosis, n (%)					
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade of disease at diagnosis, n (%)					
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior anticancer treatment, n (%)					
Any prior anti-cancer treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy post advanced/recurrent diagnosis, n (%)					
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Includes Not reported.

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynaecology and Obstetrics; ITT: intention-to-treat; RWE: real-world evidence; STD: standard deviation.

A4. Please present a breakdown of the platinum doublets received by the RWE GARNET-like population prior to their second-line (2L) therapy in a similar format to company submission (CS) Document B Table 14.

A breakdown of the platinum doublet chemotherapy regimens received in the first line (1L) for patients in the UK RWE study GARNET-like cohort (N=[redacted]) is presented in Table 3, and an equivalent table for patients in the UK RWE GARNET-like ECOG PS ≤1 cohort (N=[redacted]) is presented in Table 4.

Table 3: Platinum doublet chemotherapy regimens received in the 1L by patients in the UK RWE study GARNET-like cohort (N=[redacted])

Chemotherapy regimen	Number of patients who received platinum doublet chemotherapy in 1L, n (%) (N=[redacted]) ([redacted]%)
Carboplatin plus paclitaxel	[redacted]
Carboplatin plus PLD	[redacted]
Cisplatin plus doxorubicin	[redacted]
Carboplatin plus gemcitabine	[redacted]
Carboplatin monotherapy	[redacted]
Cisplatin plus etoposide	[redacted]
Capecitabine plus oxaliplatin	[redacted]
Carboplatin plus epirubicin	[redacted]
Bevacizumab plus carboplatin plus paclitaxel	[redacted]

Footnote: Only platinum doublet chemotherapy regimens received by at least two patients are presented in the table.
Abbreviations: 1L: first-line; PLD: pegylated liposomal doxorubicin; RWE: real-world evidence.

Table 4: Platinum doublet chemotherapy regimens received in the 1L by patients in the K RWE GARNET-like ECOG PS ≤1 cohort (N=[redacted])

Chemotherapy regimen	Number of patients who received platinum doublet chemotherapy in 1L, n (%) (N=[redacted]) ([redacted]%)
Carboplatin pls paclitaxel	[redacted]
Carboplatin plus PLD	[redacted]
Carboplatin pls etoposide	[redacted]
Cisplatin plus doxorubicin	[redacted]
Carboplatin plus gemcitabine	[redacted]

Footnote: Only platinum doublet chemotherapy regimens received by at least two patients are presented in the table.
Abbreviations: 1L: first-line; ECOG PS: Eastern Cooperative Oncology Group Performance Status; PLD: pegylated liposomal doxorubicin; RWE: real-world evidence.

A5. Document B Figure 9 only includes [redacted] people compared to the [redacted] people with an objective response rate (ORR) of Document B Table 16. Please provide an account of this. Please tabulate the data of Document B Figure 9 sufficient

to reconstruct it, and if possible and appropriate expand this tabulation to the [redacted] people with an ORR of Document B Table 16. If the mean time to CR/PR could also be given this would be helpful, and if split by CR and PR even more so.

The difference in patient numbers noted here is the result of different data cuts. [redacted] patients were included in the interim analysis 1 (IA1) which was performed using a data cut-off date of 8th July 2019. [redacted] patients were included in the IA2, using a data cut-off date of 1st March 2020.

The treatment duration of response for the [redacted] people that attained an objective response (ORR) is presented in Figure 1. The data presented for the [redacted] patients in Figure 9 in Document B were erroneously based on IA1. In line with the rest of the data presented in Document B, duration of response (DOR) data from the most recent interim analysis (IA2; data cut-off data 1st March 2020) are reflected in the figure below.

Figure 1: DOR (from time of first PR or CR) based on RECIST v1.1 in GARNET (efficacy population) (BICR)

Footnotes: Please note that this figure separates out the data for the MMR-unk population. These patients are included in the overall efficacy population as it is reasonable to assume that almost all of these patients would have tested positive for dMMR, had they been tested for dMMR, because they tested positive for MSI-H, which is the phenotypic presentation of dMMR.[2]
Abbreviations: BICR: blinded independent central review; CR: complete response; dMMR: mismatch repair deficient; DOR: duration of response; EC: endometrial cancer; MMR-unk: MMR-unknown; PD: progressive disease; PR: partial response; RECIST v1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SD: stable disease.

The tabulated data for Figure 1 is included in the reference pack within the subfolder entitled “A5. GSK Data on File”. The mean time to BOR, CR, PR and SD is presented in Table 5.

Table 5: Time to best overall response (efficacy population)

Variable	Objective response (N=[redacted])	CR (N=[redacted])	PR (N=[redacted])	SD (N=[redacted])
Mean (STD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BOR: best overall response; CR: complete response; PR: partial response; SD: stable disease; STD: standard deviation.

A6. PRIORITY Please provide the GARNET IA2 Kaplan Meier (KM) data in the same format as the following table of hypothetical data for overall survival (OS), progression-free survival (PFS) and time on treatment (ToT) for the ITT population (N=[redacted]), ITT endometrioid population (n=[redacted]) and OS, PFS, ORR and ToT for the Efficacy population (N=[redacted]) and Efficacy CR+PR population (N=[redacted]). Please present the same data restricted to the subgroups with (1) ECOG 0, (2) ECOG 1, (3) recurrent disease and ECOG 0 and (4) recurrent disease and ECOG 1.

Day	Month	Event	Censor	N at risk	S(t)
0	0.000	N=0	N=0	129	100%
3	0.099	N=0	N=2	127	100%
7	0.230	N=1	N=0	126	99%
10	0.329	N=4	N=2	120	96%
15	0.493	N=2	N=0	118	94%
etc...	etc...	etc...	etc...	etc...	etc...

The requested OS, PFS and ToT data for the GARNET ITT and efficacy populations are provided in the subfolder entitled “A6. GSK Data on File” in the reference pack submitted alongside this response. Please note that as agreed during the clarification call with the ERG and NICE on Friday 18th June, ORR was included in this question by mistake; ORR data cannot be provided in a KM format as it is not time-to-event data. As such, ORR data have not been provided in this response. GSK are currently exploring the feasibility of providing this data for the proportion of patients with endometrioid disease and will provide an update to the ERG and NICE as soon as we are able to confirm if this will be possible.

The requested data for the CR + PR population (N=[redacted]) has not been provided alongside this response, due to the reduced sample size of this population meaning that it would not be appropriate to evaluate these data or to draw any meaningful conclusions. Furthermore, as responses were ongoing for most patients in this population at the time of IA2, a response-based landmark analysis would still be immature, which would introduce additional uncertainty. Similarly, the requested ECOG subgroup data would represent a reduction in the sample size of the GARNET population, including [redacted] patients with an ECOG PS of 0, and [redacted] patients with an ECOG PS of 1, compared to the 129 patients included in the overall GARNET ITT population.

As previously described, specific identifiers to separate recurrent patients are not available

from the GARNET data, and therefore, it is not possible to obtain any data for these patients specifically.

As such, efficacy data for these subgroups have not been presented in this response for the reasons outlined above and in Question A1. GARNET trial population is not statistically powered to draw any meaningful conclusions for subgroups of the ITT and efficacy populations, and the GARNET ITT population is already a biomarker-specific subpopulation of the overall population of patients with EC, for which there is significant unmet need across all patients with dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy.

A7. Please tabulate the GARNET IA2 reasons for OS events, OS censoring events, PFS events, PFS censoring events, ToT events, ToT censoring events and the number of people these apply to. Please provide this as disaggregate as possible, follow the classification of reasons of GARNET and do not follow the hypothetical reasons listed below. Where there may be ambiguity about the definition of a reason please provide a full description.

	OS		PFS		ToT	
Reason	Event	Censor	Event	Censor	Event	Censor
Death	N=???	n.a.	N=???	n.a.	N=???	N=???
Progression	N=???	N=???	N=???	n.a.	N=???	N=???
SAE	N=???	N=???	N=???	N=???	N=???	N=???
Study withdrawal	N=???	N=???	N=???	N=???	N=???	N=???
Etc…						

The patient disposition for patients in the ITT population of the GARNET trial is presented below in Table 6. Unfortunately, the additional information requested as part of this question is not available.

Table 6: GARNET ITT population patient disposition

Variable reason [n (%)]	**Number of patients (N=129)**
Discontinued treatment	[redacted]
Adverse event	[redacted]
Confirmed disease progression	[redacted]
Risk to patients as judged by the Investigator and/or Sponsor	[redacted]
Severe noncompliance with the protocol as judged by the Investigator and/or Sponsor	[redacted]
Patient request	[redacted]
Patient pregnancy	[redacted]
Sponsor decision to terminate study	[redacted]
Based on clinical criteria by Investigator	[redacted]
Other	[redacted]

Discontinued study	[redacted]
Withdrawal of consent	[redacted]
Lost to follow-up	[redacted]
Sponsor decision to terminate study	[redacted]
Death	[redacted]
Other	[redacted]
Subjects treated beyond initial disease progression	[redacted]
Died while on study	[redacted]
Disease progression	[redacted]
Adverse event	[redacted]
Unknown	[redacted]
Other	[redacted]

Abbreviations: ITT: intention-to-treat.

A8. PRIORITY Please provide the RWE GARNET-like KM data in the same format as the table of hypothetical data requested under A6 above for OS, time to next therapy (TTNT) and time to treatment discontinuation (TTD). As under A6, please present this separately for all populations, the four subgroups of A6 and the additional two subgroups of (5) ECOG undefined, (6) ECOG undefined recurrent. Please also present this restricted to all people with endometrioid disease and the six subgroups.

The pseudo-IPD for OS, TTNT and TTD detailing all events (including censored events) for both the GARNET-like and the GARNET-like ECOG PS ≤1 UK RWE study populations are included within the reference pack, in the subfolder entitled “A8. GSK Data on File”.

As outlined in the response to Question A2, data for patients with endometrioid histology are not currently available from the UK RWE study, although GSK are exploring the feasibility of providing these data from Public Health England.

For the same reasons outlined in response to Questions A1 and A2, additional data for the subgroups requested in Question A6, and for additional groups of patients stratified by ECOG undefined status will not be presented as they are not considered relevant to this appraisal.

A9. Please provide the raw unmatched RWE GARNET-like KM data in the same format as the table of hypothetical data requested under A6 above for OS, TTNT and TTD separately for people receiving carboplatin+paclitaxel (N=[redacted]), carboplatin+PLD (N=[redacted]), PLD monotherapy (N=[redacted]), paclitaxel monotherapy (N=[redacted]), carboplatin monotherapy (N=[redacted]) and cisplatin+doxorubicin (N=[redacted]). The four subgroups of A6 are not required.

The raw unmatched UK RWE study GARNET-like KM data for OS, TTNT and TTD

separated by chemotherapy regimen are presented in the Excel file in the subfolder included within the reference pack entitled “A9. GSK Data on File”.

In line with the response to Question A3, data have only been provided for treatments which were prescribed to ≥5% of patients in the GARNET-like population. Cisplatin plus doxorubicin was prescribed to <5% of these patients, and notably, it was not listed in the NICE final scope as a relevant comparator. As such, survival outcomes for patients receiving cisplatin plus doxorubicin were not explored and are therefore not presented.

A10. PRIORITY Please provide two additional matching-adjusted indirect comparison (MAIC) analyses for the GARNET ITT endometrioid population with: (1) RWE GARNET-like population restricted to those with endometrioid disease; and, (2) RWE GARNET-like ECOG 0/1 population restricted to those with endometrioid disease. For each of these analyses please provide the resulting KM OS and PFS data for each arm in the same format as that requested under A6 above. NICE and the ERG realise that if this has not already been undertaken there will need to be flexibility on the timing of the provision of this.

As highlighted previously in response to Questions A1 and A2, subgroup analyses based on endometrioid disease status are not considered relevant to this appraisal and therefore the requested MAIC analyses for this question have not been conducted.

A11. Please tabulate the KM data of Document B figures 23, 24, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37 separately by arm, excluding the unadjusted GARNET arm KM data already requested in other clarification questions, in the same format as that requested under A6 above. Please also supply this data equivalent to Document B figures 23, 24, 26, 27 for the MAIC of GARNET with the RWE GARNET-like ECOG 0/1 population. OS and TTNT for the unadjusted GARNET-like UK RWE study population and the GARNET-like ECOG PS ≤1 RWE population have been provided in response to Question A8.

The requested data for the following KM curves from the UK RWE study MAICs are provided in the reference pack subfolder entitled “A11. GSK Data on File”:

- OS (GARNET, versus GARNET-like, Scenario 1)
- OS (GARNET, versus ECOG PS ≤1, Scenario 1)
- OS (GARNET, versus GARNET-like, Scenario 2)
- OS (GARNET, versus ECOG PS ≤1, Scenario 2)
- PFS (GARNET, versus GARNET-like, Scenario 1)
- PFS (GARNET, versus ECOG PS ≤1, Scenario 1)
- PFS (GARNET, versus GARNET-like, Scenario 2)
- PFS (GARNET, versus ECOG PS ≤1, Scenario 2)

The requested data for the following KM curves from the MAICs versus the published literature are provided in the reference pack subfolder entitled A11.

- OS (GARNET, versus Julius et al. [2013])

- OS (Julius et al. [2013])
- OS (GARNET, versus McMeekin et al. [2015])
- OS (McMeekin et al. [2015])
- PFS and OS (GARNET, versus Rubinstein et al. [2019])
- PFS and OS (Rubinstein et al. [2019])
- PFS and OS (GARNET, versus Makker et al. [2013])
- PFS and OS (Makker et al. [2013])
- PFS and OS (GARNET, versus Mazgani et al. [2008])
- PFS and OS (Mazgani et al. [2008])

The requested data for the following KM curves from the ITC between GARNET and ZoptEC are provided in the reference pack subfolder entitled A11. Please note it was currently only possible to do this for the unweighted PFS and OS:

- PFS and OS (GARNET, following exclusion of patients to align more closely with ZoptEC)
- PFS and OS (ZoptEC, following exclusion of patients to align more closely with GARNET)

GSK are currently in the process of obtaining the equivalent data for the adjusted OS curves, and will provide this as soon as possible:

- OS (GARNET, following IPTW versus ZoptEC)
- OS (ZoptEC, following IPTW versus GARNET)

A12. PRIORITY

a) Please confirm that the Document B Figure 16 W3 to W96 are for people in PFS. Please confirm that end-of-treatment (EOT) to survival follow-up 5 (SUVF5) are for people who have finished treatment. Please define SFU and SUVF1 to SUVF5 in terms of weeks since EoT, to the extent possible. Please clarify if all people contributing to EoT and subsequent quality of life (QoL) assessments have necessarily progressed or have only necessarily ceased treatment.

GSK can confirm that the data presented in Document B Figure 16 for W3 to W96 are for patients in who had a Baseline PRO assessment and at least one follow-up PRO assessment reported (per the supplemental SAP), and the data presented for end-of-treatment (EoT) to survival follow-up 5 (SUVF5) are for patients who have discontinued treatment from dostarlimab. The definitions for SFU and SUVF1–F5 are as follows:

- **SFU**: 90 days (± 7 days) after the last date of study drug administration. After the 90-day safety follow-up visit, patients will enter the post-treatment follow-up period for telephone assessment for survival status every 90 days.
- **SUVF1–F5:** 90 days (± 14 days) from the safety follow-up visit.

Patients contributing to the EoT datapoint and subsequent QoL assessments may have

experienced disease progression, but not necessarily. All patients will have discontinued treatment at this stage.

b) For Document B Figure 16 please tabulate the values of each point and its 95% confidence interval and also tabulate the equivalent values for the ITT population, and also tabulate their equivalents for the EQ-5D-5L cross walked to the UK social tariff. Please also tabulate the GARNET EQ-5D-5L cross walked to the UK social tariff in the following format, separately for (1) the ITT population, (2) the Efficacy population and (3) the ITT advanced at baseline population.

	Number of people		Mean QoL	
Timepoint	Eligible	Reporting	Baseline	Timepoint
Baseline	N=?	N=?	μ=?	μ=?
W3	N=?	N=?	μ=?	μ=?
W9	N=?	N=?	μ=?	μ=?
etc…	N=?	N=?	μ=?	μ=?
W96	N=?	N=?	μ=?	μ=?
EOT	N=?	N=?	μ=?	μ=?
SUV	N=?	N=?	μ=?	μ=?
SUVF1	N=?	N=?	μ=?	μ=?
etc…	N=?	N=?	μ=?	μ=?
SUVF5	N=?	N=?	μ=?	μ=?

EQ-VAS data

A summary of the tabulated data underlying Document B, Figure 16 is presented in Table 7. An equivalent figure for the GARNET ITT population is presented in Figure 2, and the equivalent data and associated 95% confidence intervals are presented in Table 8.

Table 7: Adjusted mean change from baseline in EQ-VAS score (GARNET efficacy population)

Visit	No of pts at visit	Est	Lower	Upper
Week 3	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 30	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
Week 42	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]
Week 54	[redacted]	[redacted]	[redacted]	[redacted]

Week 60	[redacted]	[redacted]	[redacted]	[redacted]
Week 66	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]
Week 78	[redacted]	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]	[redacted]
Week 90	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]
End of Treatment	[redacted]	[redacted]	[redacted]	[redacted]
Safety Follow Up	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow Up 1	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow Up 2	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow Up 3	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 4	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 5	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-VAS: EuroQol Visual Analogue Scale.

Figure 2: Adjusted mean change from Baseline in EQ-VAS (GARNET ITT population)

Abbreviations: EQ-VAS: EuroQol Visual Analogue Scale; ITT: intention-to-treat.

Table 8: Adjusted mean change from baseline in EQ-VAS (GARNET ITT population)

Visit	No of pts at visit	Est	Lower	Upper
Week 3	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Week 18	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 30	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
Week 42	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]
Week 54	[redacted]	[redacted]	[redacted]	[redacted]
Week 60	[redacted]	[redacted]	[redacted]	[redacted]
Week 66	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]
Week 78	[redacted]	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]	[redacted]
Week 90	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]
End of Treatment	[redacted]	[redacted]	[redacted]	[redacted]
Safety Follow Up	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow Up 1	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow Up 2	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow Up 3	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 4	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 5	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-VAS: EuroQol Visual Analogue Scale; ITT: intention-to-treat.

EQ-5D data

The requested equivalent data, relating to the change from baseline in EQ-5D index score (mapped from EQ-5D-5L responses using the Van Hout algorithm and UK tariff) are shown in Figure 3 and Table 9 for the GARNET efficacy population, and in Figure 4 and tabulated in Table 10 for the GARNET ITT population.

Figure 3: Adjusted mean change from baseline in EQ-5D utility score (GARNET efficacy population)

Table 9: Adjusted mean change from baseline in EQ-5D utility score (GARNET efficacy population)

Visit	Est	Lower	Upper
Week 3	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Week 30	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]
Week 42	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]
Week 54	[redacted]	[redacted]	[redacted]
Week 60	[redacted]	[redacted]	[redacted]
Week 66	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]
Week 78	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]
Week 90	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]
End of Treatment	[redacted]	[redacted]	[redacted]

Safety Follow Up	[redacted]	[redacted]	[redacted]
Survival Follow Up 1	[redacted]	[redacted]	[redacted]
Survival Follow Up 2	[redacted]	[redacted]	[redacted]
Survival Follow Up 3	[redacted]	[redacted]	[redacted]
Survival Follow-up 4	[redacted]	[redacted]	[redacted]
Survival Follow-up 5	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D: EuroQol 5 dimensions.

Figure 4: Adjusted mean change from baseline in EQ-5D utility score (GARNET ITT population)

Table 10: Adjusted mean change from baseline in EQ-5D utility score (GARNET ITT population)

Visit	Est	Lower	Upper
Week 3	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Week 30	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]
Week 42	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]
Week 54	[redacted]	[redacted]	[redacted]

Week 60	[redacted]	[redacted]	[redacted]
Week 66	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]
Week 78	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]
Week 90	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]
End of Treatment	[redacted]	[redacted]	[redacted]
Safety Follow Up	[redacted]	[redacted]	[redacted]
Survival Follow Up 1	[redacted]	[redacted]	[redacted]
Survival Follow Up 2	[redacted]	[redacted]	[redacted]
Survival Follow Up 3	[redacted]	[redacted]	[redacted]
Survival Follow-up 4	[redacted]	[redacted]	[redacted]
Survival Follow-up 5	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D: EuroQol 5 dimensions; ITT: intention-to-treat.

Numbers of observations and observed EQ-5D index and VAS scores in the ITT population by study visit are reported in Table 11.

Table 11: Observed EQ-5D index scores (mapped from EQ-5D-5L) and VAS scores and numbers of patient observations by study visit (GARNET ITT population)

	Mapped EQ-5D index score			**EQ-VAS**		
Visit	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 18 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Safety Follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: Each cycle is 3 weeks.
Abbreviations: EQ-5D-5L: EuroQol 5 dimensions 5 levels; EQ-VAS: EuroQol Visual Analogue Scale; ITT: intention-to-treat; SD: standard deviation.

Numbers of observations and observed EQ-5D index and VAS scores in the efficacy population by study visit are reported in Table 12.

Table 12: Observed EQ-5D index scores (mapped from EQ-5D-5L) and VAS scores and numbers of patient observations by study visit (GARNET efficacy population)

	Mapped EQ-5D index score			EQ-VAS		
Visit	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 18 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety Follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival Follow-up 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: Each cycle is 3 weeks.
Abbreviations: EQ-5D-5L: EuroQol 5 dimensions 5 levels; EQ-VAS: EuroQol Visual Analogue Scale; SD: standard deviation.

As previously outlined in Question A1, specific identifiers to separate groups of patients with recurrent or advanced disease are not available in GARNET, and therefore, it is not possible to provide EQ-5D results for patients in the ITT population with advanced disease at baseline.

A13. PRIORITY Regarding MAICs, please present the original full regression models used and results, including p-values and each of the backward elimination steps required to arrive at the final models applied to estimate each of the MAIC-adjusted KM curves. Please present these for both (1) the GARNET vs RWE GARNET-like MAIC, and (2) the GARNET vs RWE GARNET-like ECOG 0/1 MAIC.

The full regression models and results, before and after backwards stepwise elimination, used to arrive at the final model for each of the MAIC-adjusted KM curves are available in the reference pack titled “A13. GSK Data on File”.

Each Excel file starts with the full model and then summarises the steps from the model selection. A summary of the final model is presented at the end of each document.

The covariates were defined as previously described in Appendix D.5.1. The starting model contained the following categorical variables: age at registry diagnosis, performance status at registry diagnosis, ethnicity, FIGO stage, tumour grade, histology, prior surgery.

A14. Please provide the number and baseline characteristics of people receiving hormone therapy as second-line treatment in advanced or recurrent setting in the UK RWE GARNET-like population, had they not been excluded (The ERG is aware that use of hormone therapy was incompletely captured).

As explained in the clarification call with the ERG and NICE on Friday 18th June, it was not the case that patients receiving hormone therapy were excluded from the UK RWE study GARNET-like cohort, rather hormone therapy was not accurately captured in the NCRAS database. Within this dataset, drugs which are delivered ‘outside’ of an oncology environment (e.g. in surgical clinics or in primary care) are often poorly recorded.

Patients receiving hormone therapy dispensed in primary care or community pharmacies would therefore have been poorly captured in this analysis, with a previous study estimating more than 80% of endocrine therapies captured in an alternative NHS England (NHSE) dataset (Cancer Waiting Times) had not been captured in systemic anti-cancer therapy database (SACT).[3] As a result, only [redacted] patients [redacted] were recorded as receiving hormone therapy in the UK RWE study, and these patients were included in the GARNET-like cohort. Given the presentation of baseline characteristics for these two patients would not be meaningful, they are not presented here.

A15. Number of prior lines of therapy, CS Document B Table 7. Please confirm if lines of treatment have the same definition in GARNET and UK RWE. Please confirm if the lines of treatment noted refer to those received in recurrent and advanced setting or in pre-recurrent and advanced setting. Please confirm if all prior therapies for the GARNET population are platinum-based therapies. Please confirm if platinum-based therapy is the last line of therapy prior to dostarlimab for all GARNET participants.

Yes, the definition of lines of prior therapy is aligned between GARNET and the UK RWE study: in both cases, lines of prior therapy refers to therapies received in the recurrent or advanced disease settings only. By design, slight differences exist between GARNET, where this data was directly available for patients, and the UK RWE study, which uses retrospective data from the SACT dataset.

GARNET: The number of lines of prior therapy is defined as: “Number of prior regimens for metastatic disease, excluding neo-adjuvant regimens, adjuvant regimens and hormonal agents.”

RWE: Prior lines of therapy were derived using the algorithm outlined in Appendix O.1, Page 286 of the Company Submission Appendices.

All prior anticancer therapy and the last line of therapy received prior to dostarlimab by patients enrolled in the GARNET ITT population are presented in the subfolder included within the reference pack, titled “A15. GSK Data on File”. As per the inclusion criteria of the GARNET trial, participants had to have “progressed on or after platinum doublet therapy”, however it was not compulsory that the last line of therapy prior to dostarlimab had to be a platinum-based doublet therapy.

Except for one patient that did not receive prior platinum-based chemotherapy (GARNET CSR, Section 10.2, Protocol Deviations), all patients included in the GARNET trial ITT population had received a platinum-based doublet therapy prior to dostarlimab.

As per the inclusion criteria of the RWE study, participants had to have “confirmed receipt of platinum-doublet therapy” post-advanced/recurrent index date. The UK RWE study GARNET-like cohort (N=[redacted]) are those patients who have one prior line of treatment i.e. have received one line of platinum doublet chemotherapy, progressed, and received further second line treatment.

A16. Definition of recurrence – Please confirm if UK RWE recurrent population had some sort of radiographic evidence to confirm recurrence; and recurrence definition did not rely on only 90 days interval between treatments. UK RWE study Document B Page 49 - Table 10 Footnotes – “patients who were FIGO Stage I/II and received surgery, systemic anti-cancer therapy or radiation

therapy and then had a treatment gap greater than 90 days, followed by treatment with any treatment".

As outlined in Document B, Section B.2.11.3, the NCRAS database does not collect data (including radiographic evidence), for progression, remission or recurrence of disease. As such, it was necessary to use proxy measures for PFS and disease recurrence when analysing the data obtained from the UK RWE study. Probable recurrence was defined as the first occurrence of a gap >90 days between any consecutive treatments (surgery, systemic therapy, radiation therapy including brachytherapy), with an index date for probable recurrent EC being equal to the date of treatment resumption following the >90-day gap.

To calculate gaps in treatment, treatment events were abstracted from their respective sources and sorted by ascending date. Patients diagnosed at Stage I or Stage II and who did not experience a gap between treatments >90 days in direction were excluded.

The 90-day gap was decided upon as the number of days to determine recurrence, as this aligns with the number of days used in the algorithm used to derive lines of therapy, which also uses a treatment gap of 90 days to determine all subsequent lines of therapy.

In order to explore the impact of defining recurrence by a gap >90 days, a *post-hoc* sensitivity analysis was conducted, exploring the differences in the number of patients when recurrence was defined by >90 days versus >180 days. The results are presented in Table 13. The sensitivity analysis results give confidence that the recurrent patients captured in the RWE cohort were robust, with only small differences between the patient populations when recurrence was defined as >180 days.

Table 13: Differences between recurrence defined by 90 or 180 days

	Recurrence rule		
Cohort	**>90 days**	**>180 days**	**Difference, N (%)**
GARNET-like population of patients with advanced/recurrent EC	[redacted]	[redacted]	[redacted]
GARNET-like ECOG PS ≤1 population of patients with advanced/recurrent EC	[redacted]	[redacted]	[redacted]

Abbreviations: EC: endometrial cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

To validate the definition of recurrence, the number of patients identified in the UK RWE study was compared to the estimated incidence of patients with recurrent EC based on published epidemiological estimates for the UK. The six-year incidence of EC, based on Cancer Research UK, was estimated at 12,058 patients (assuming that ~95% of patients with uterine cancer have EC). Of these, 30,922 patients had stage I EC, and 3,135 patients had stage II EC, representing a total of 34,057 patients with stage I/II EC. As detailed in Document B, Section B.1.3.3, approximately 13% of these patients would be expected to experience disease recurrence.[4, 5]

In the UK RWE study, a total of [redacted] patients were identified with recurrent EC in six years (2013–2018) (prior to the application of GARNET-like inclusion/exclusion criteria). This equates to [redacted]% of the patient population with stage I/II EC estimated from Cancer Research UK, a proportion which is well-aligned with the estimated 13% based on the

published literature, providing further confidence that the definition of recurrence in the UK RWE study was robust.[4, 5]

Further details on the algorithm used to derive the lines of therapy are presented in the Company Submission Appendix O.1.

A17. Please provide information on baseline characteristics in ZoptEC (ITT population; N=255) in the same format as Appendix Page 111 - Table 40: Comparison of baseline characteristics in ZoptEC and GARNET.

A summary of the baseline characteristics of patients receiving doxorubicin in the ZoptEC ITT population (N=255) and patients receiving dostarlimab in the GARNET ITT population (N=129) is provided in Table 14.

Table 14: Summary of baseline characteristics for patients receiving doxorubicin in ZoptEC (N=255) and dostarlimab in GARNET (N=129)

Characteristic	Patients in the doxorubicin arm of ZoptEC[6-8] (N=255)	GARNET ITT population (N=129)
Mean age, years (STD)	[redacted]	[redacted]
Median age, years (range)	[redacted]	[redacted]
Age group, n (%)		
<65 years	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]
Unknown[b]	[redacted]	[redacted]
BMI, kg/m^2		
Median, (range)	[redacted]	[redacted]
ECOG PS, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Histology at diagnosis, n (%)		
Endometroid type I	[redacted]	[redacted]
Serous carcinoma	[redacted]	[redacted]
Clear cell carcinoma	[redacted]	[redacted]
Squamous cell carcinoma	[redacted]	[redacted]
Other/Unspecified	[redacted]	[redacted]

Undifferentiated carcinoma	[redacted]	[redacted]
Mixed carcinoma	[redacted]	[redacted]
FIGO stage at baseline, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Advanced (FIGO III or IV)	[redacted]	[redacted]
Metastatic	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]
Prior lines of therapy		
One prior treatment	[redacted]	[redacted]
Two prior treatments	[redacted]	[redacted]
Three prior treatments	[redacted]	[redacted]
Four prior treatments	[redacted]	[redacted]
Prior adjuvant chemotherapy	[redacted]	[redacted]
Prior surgery	[redacted]	[redacted]
Prior radiotherapy	[redacted]	[redacted]

Footnotes: [a] Includes Native Hawaiian or Other Pacific Islander. b Includes 'Not reported'.
Abbreviations: BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynaecology and Obstetrics; ITT: intention-to-treat; NR: not reported; STD: standard deviation.

A18. Please provide more information on the rationale for excluding people with follow-up greater than 36 months in the ZoptEC study (Appendices Page 116, Table 44:). Please provide the rationale for not using the same exclusion criteria for RWE GARNET-like population.

Patients with a follow-up greater than 36 months in the ZoptEC study were excluded from the ZoptEC ITC in order to align to the patient population of the GARNET trial more closely within this one-to-one comparison, by ensuring that patients were observed for similar periods of time given the differences in design between the two trials. Only [redacted] patients in the ZoptEC ITC were excluded for this reason (Table 44, Appendix D.5.2).

The sensitivity analysis presented in Table 51, Appendix D.5.2 shows that when patients were not excluded from GARNET and ZoptEC prior to IPTW (except for [redacted] patient without baseline ECOG PS who had to be excluded), the OS HR between dostarlimab and doxorubicin was [redacted] ([redacted], [redacted]), highly similar to the OS HR of [redacted] ([redacted], [redacted]) calculated in the base case analysis (Table 26, Document B, Section B.2.7.2.1). As such, it is reasonable to conclude that the exclusion of these patients from the ZoptEC study prior to IPTW did not have a meaningful impact on results.

The same exclusion criterion was not applied to the RWE study, so as to try and include as

much of the data as possible given these data included multiple regimens and much greater follow-up.

A19. Appendices Table 31 regression output: the title indicated n=[redacted] (as would be expected for RWE GARNET-like population), but data in the table suggest that only [redacted] people were included in the analysis. Please clarify.

The discrepancy in patient numbers between the UK RWE study GARNET-like population ([redacted]) and the regression output (n=[redacted]) is due to the type of variable used to capture FIGO stage in the UK RWE study data analysis. FIGO stage as a variable is recorded in two ways in the NCRAS database:

1. The STAGE_BEST variable is usually provided by NHS Trusts, but registration staff are trained to derive this information from pathology and clinical investigations when necessary. The STAGE_BEST FIGO stage variable was used to define the n=[redacted] patient cohort captured in the GARNET-like cohort.

2. The actual FIGO stage data are provided solely by NHS Trusts, and there are no means of deriving this if the information is missing. The actual FIGO stage data were used to define the n=[redacted] patient cohort captured in the regression analysis.

Actual FIGO stage was used in the UK RWE study regression analysis to best align with the GARNET trial regression analysis, which also used actual FIGO stage data. The outputs of the UK RWE study regression analysis, based on the cohort of n=[redacted] patients, were then used to inform the MAIC analysis of the n=[redacted] GARNET-like patient cohort.

Table 15 below illustrates the level of concordance between the STAGE_BEST FIGO stage variable and the actual FIGO stage variable in the NCRAS database for the entire UK RWE study population (N=[redacted]). This table shows that for the most part there is a high level of agreement between the two variables.

Table 15: Illustration of the level of concordance between STAGE_BEST FIGO stage and actual FIGO stage variables in the NCRAS database for the UK RWE study (N=[redacted])

PATIENT_COUNT	STAGE_BEST FIGO stage	Actual FIGO stage
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: FIGO: International Federation of Gynaecology and Obstetrics; NCRAS: National Cancer Registration and Analysis Service.

A20. Please provide information on time since initial diagnosis at trial baseline for GARNET ITT and ZoptEC populations and the equivalent data for GARNET-like RWE population.

GARNET: The median time since cancer diagnosis at trial baseline was [redacted] years (range: [redacted], [redacted]) for the GARNET ITT population at IA2.

ZoptEC: The median time since cancer diagnosis was [redacted] months (range: [redacted], [redacted] months) for patients assigned to doxorubicin in the ZoptEC study.[9]

UK RWE study GARNET-like population: Time since diagnosis data are unfortunately not available from the UK RWE study. The year of diagnosis for each patient is available, and these data are presented in Table 16. It should be noted that 'diagnosis' in the NCRAS database refers to registry diagnosis (i.e. the date a patient is entered in the NCRAS registry), and not necessarily the date of cancer diagnosis. As the date of cancer diagnosis is not available for the UK RWE study GARNET-like population, the year of registry diagnosis represents the best available proxy.

Table 16: Year of diagnosis for patients in the UK RWE study GARNET-like population

Year of diagnosis, n (%)	UK RWE study GARNET-like population (N=[redacted])

2013	[redacted]
2014	[redacted]
2015	[redacted]
2016	[redacted]
2017	[redacted]
2018	[redacted]

Abbreviations: RWE: real-world evidence; UK: United Kingdom

A21. Please provide information on the median duration of follow-up for GARNET ITT population at IA2.

The median duration of follow up for the GARNET ITT population at IA2 was [redacted] months.

Section B: Clarification on cost-effectiveness data

B1. PRIORITY For Tables 51, 53, 56, 58 and 62 clarify the uncertainty/range around each table cell. Please clarify the method of eliciting these values and all data that was communicated to the experts prior to them providing their opinions; e.g. GARNET OS KM S(t), OS KM S(t) 95% confidence limits, GARNET OS KM N at risk, RWE OS KM S(t), OS KM S(t) 95% confidence limits, RWE OS KM N at risk etc. prior to them making their estimates. If possible, please provide copies of the background briefing and questionnaire, together with an outline of how the elicitation exercise was conducted; e.g. online questionnaire, individual telephone interviews, group meeting.

Survival estimates

On 26th January 2021, GSK conducted a virtual advisory board with seven clinical experts, including clinical and medical oncologists, gynae-oncology surgeons, a gynaecological histopathologist and a gynaecology clinical nurse specialist, all of whom are involved in the therapy of women with advanced/recurrent EC in the UK.

During this meeting, the clinicians were presented with unpublished KM data for OS and PFS for patients receiving dostarlimab in GARNET, and patients with current clinical management based on the UK RWE study.

Throughout the advisory board, the clinicians were asked a number of polling questions via digital interaction using Slido. The estimates in Table 51, 53, 56 and 58 were derived from the answers to the following questions:

- Based on your clinical experience, the presented GARNET data, and RWE – please provide an estimate of the percentage of the relevant patient population, post treatment with dostarlimab that will be alive at 3/5/10/15/20 years

- Based on your clinical experience, the presented GARNET data, and RWE – please provide an estimate of the percentage of the relevant patient population, post treatment with current 2L chemotherapy options that will be alive at 5/10/15/20 years

- Based on your clinical experience, the presented GARNET data, and RWE – please provide an estimate of the percentage of the relevant patient population, post treatment with dostarlimab that will be progression-free at 3/5/10/15/20 years

- Based on your clinical experience, the presented GARNET data, and RWE – please provide an estimate of the percentage of the relevant patient population, post treatment with current 2L chemotherapy options that will be progression-free at 5/10/15/20 years

The clinicians provided a single estimate in response to each question for each timepoint, which are presented in full in Document B, alongside the mean, which was calculated as detailed in Document B. Consequently, there are no further details about the uncertainty or ranges associated with the estimates presented in these tables.

The pre-read materials and slides presented during these calls are provided in the reference pack accompanying this document and as part of the response to Question C1.

Time on treatment assumptions

The derivation of the time on treatment assumptions incorporated in the base case cost-effectiveness analysis are described in more detail in response to Question B3.

B2. PRIORITY

a) Please provide a full account of the GARNET QoL statistical analyses together with copies of any relevant internal GSK report(s) relating to this, including but not limited to method, population group baseline characteristics (N=[redacted]), N observations through time, models explored, coefficients, s.e. and p values, goodness of fit with the goodness of fit measures expanded to include some that take into account of the number of explanatory variables; e.g. R¯^2, AIC, etc..

Within the GARNET ITT population, EQ-5D-5L responses were collected from [redacted] patients at both study baseline and a minimum of one post-baseline visit. A series of regression models were specified to estimate patient utility scores corresponding to health states (progression-free and progressed disease) used in the economic model and to explore the inclusion of additional potentially meaningful factors including proximity to death. Baseline characteristics of the N=[redacted] GARNET E5-5D subpopulation are presented in Table 17.

Table 17: Baseline characteristics of the GARNET EQ-5D subpopulation (N=[redacted])

Characteristic	Value
Age, years (mean, STD)	[redacted]

Height, cm (mean, STD)	[redacted]
Weight, kg (mean, STD)	[redacted]
BMI (mean, STD)	[redacted]
ECOG performance status (n, %)	
0	[redacted]
1	[redacted]
Histology at diagnosis (n, %)	
Adenocarcinoma	[redacted]
Clear Cell Carcinoma	[redacted]
Endometrial Adenocarcinoma	[redacted]
Endometrial Carcinoma Type II	[redacted]
Endometrioid Adenocarcinoma	[redacted]
Endometrioid Carcinoma Type I	[redacted]
Mixed Carcinoma	[redacted]
Serous Carcinoma	[redacted]
Undifferentiated Clear Cell Carcinoma	[redacted]
MSI/MMR status (n, %)	
MSI-H/dMMR	[redacted]
MSI-H/MMR unknown	[redacted]

Abbreviations: BMI: body mass index; dMMR: mismatch repair deficient; ECOG: Eastern Cooperative Oncology Group; EQ-5D: EuroQoL-5 dimensions; MRR: mismatch repair; MSI(-H): microsatellite-instability(-high); STD: standard deviation.

Guidance published by NICE recommends that utilities are estimated using the generic EQ-5D-3L instrument, using a validated mapping function where the 5L rather than 3L version of the instrument has been collected. As a first step, EQ-5D-3L utility scores according to the UK tariff were estimated from EQ-5D-5L responses for each patient visit using a cross-walk index value calculator developed by Van Hout *et al*. Numbers of responses and mean estimated utility values by study visit are reported, along corresponding EQ-VAS responses, in Table 11 (Clarification Question 12b).

Regression models were specified to estimate health state-specific utilities using STATA Version 14.2. To account for correlation between repeated measures from individuals at separate time points, a generalised estimating equation (GEE) approach was adopted using patient identifiers to identify repeated sampling from individuals.

A primary aim was to generate estimates of utilities according to patients' progression status (pre-progression or post-progression) in line with the health states defined in the economic model. For these models, explanatory variables were restricted to patients' baseline utility and progression status according to RECIST 1.1 criteria. Alternative models explored the inclusion of clinically-relevant explanatory variables including patient age, ethnicity and baseline ECOG performance status at baseline.

As a second set of analyses, time to death was included as an explanatory variable to capture expected deteriorations in health status in the weeks or months prior to death. Two

broad specifications were explored: in the first, proximity to death was defined as a dichotomous (binary) variable, identifying observations within/beyond a specified number of model cycles (21-day intervals) from death. Under the second approach, time to death was specified as a discrete ordinal set of ranges.

Optimal model choice was assessed in terms of goodness of fit and the distribution of patient observations across the range of covariates explored. Since the GEE approach corresponds to quasi-likelihood rather than maximum likelihood, the Quasi-likelihood under the Independence model Criterion (QIC) measure was adopted rather than AIC to assess relative goodness-of-fit penalising for model complexity. R-squared values were approximated according to the squared correlation between observed and predicted values.

The output of regression models predicting utilities according to progression status are shown in Table 18. None of the baseline characteristics explored (age, race and baseline ECOG score) were found to be statistically significant when added as covariates. Patient advanced/recurrent status at baseline was not available from the dataset explored. Model 1 was selected as the most appropriate base model according to QIC (lowest value), and covariate significance. R^2 was found to be comparable across models except where race was included (data missing for 15 patients).

Table 18: Results of regression analyses predicting utilities by progression status

	Model 1			Model 1a			Model 1b			Model 1c		
	Coeff	SE	P	Coeff	SE	P	Coeff	SE	P	Coeff	SE	P
Baseline utility	[redacted]											
Progressed	[redacted]											
Age	[redacted]											
Race (white)	[redacted]											
Baseline ECOG 1	[redacted]											
Constant	[redacted]											
Observations	[redacted]											
Groups	[redacted]											
R^2	[redacted]											
QIC	[redacted]											

Abbreviations: Coeff: coefficient; ECOG: Eastern Cooperative Oncology Group; SE: standard error; QIC: Quasi-likelihood under the Independence model Criterion.

The output of the regressions including time to death as a dichotomous explanatory variable are shown in Table 19. Of these, a 5-cycle threshold was considered most appropriate as discussed below.

Table 19: Results of regression analyses predicting utilities by progression status and time to death (dichotomised)

	[cycles]=1			[cycles]=2			[cycles]=3		
	Coeff	SE	P	Coeff	SE	P	Coeff	SE	P
Baseline utility	[redacted]								
Time to death>[cycles]	[redacted]								
Progressed	[redacted]								
Constant	[redacted]								
Observations	[redacted]								
Groups	[redacted]								
R^2	[redacted]								

QIC									
	[cycles]=4			**[cycles]=5**			**[cycles]=6**		
	Coeff	**SE**	**P**	**Coeff**	**SE**	**P**	**Coeff**	**SE**	**P**
Baseline utility									
Time to death>[cycles]									
Progressed									
Constant									
Observations									
Groups									
R^2									
QIC									
	[cycles]=7			**[cycles]=8**			**[cycles]=9**		
	Coeff	**SE**	**P**	**Coeff**	**SE**	**P**	**Coeff**	**SE**	**P**
Baseline utility									
Time to death>[cycles]									
Progressed									
Constant									
Observations									
Groups									
R^2									
QIC									

Abbreviations: Coeff: coefficient; SE: standard error; QIC: Quasi-likelihood under the Independence model Criterion.

For the time to death analyses, base model selection considered not only statistical fit (according to R^2 and QIC) but also face validity according to the number and distribution of patients according to the threshold assigned to denote proximity to death.

The lowest QIC values were associated with time-to-death thresholds of nine, eight and one model cycles. However, patient data included only two observations within one cycle of death (Figure 5). On the other hand, increasing the time-to-death threshold to nine model cycles (27 weeks) required 225 observations (29%) to be excluded from estimates, since observations could only be included where (a) the date of death was known (median overall survival was not reached at data cut-off) or (b) the time between the observation and last recorded date alive exceeded the time-to-death threshold assigned. On this basis, a 5-cycle threshold was considered to be an appropriate compromise in terms of model fit (Table 19) and the acceptability of overall and state-specific sample sizes (Figure 5).

Figure 5: Predicted utility score by progression status and time to death (dichotomised)

Abbreviations: Cyc: cycle; EQ-5D: EuroQoL 5-dimensions; PD: progressed disease; PFS: progression-free survival; TTD: time to death.

Exploratory analyses specifying patient time to death as an ordinal range and modelled as factor variables (Figure 6) were not considered appropriate due to the limited numbers of observations at discrete time points close to death, as discussed above. However, visual inspection of predicted scores using this method did support the application of a 5-cycle time-to-death threshold according to the magnitude of differences in predicted utilities for adjacent time-to-death states.

Figure 6: Predicted utility score by progression status and time to death (ordinal)

Abbreviations: EQ-5D: EuroQoL 5-dimensions; PD: progressed disease; PFS: progression-free survival.

b) Please outline why pseudonymised personal identifiers were used rather than actual personal identifiers given that Figure 16 makes no mention of this, and how the pseudonymised personal identifiers were arrived at.

Unique patient IDs (SUBJID field in the GARNET datasets) were used to identify individuals, with no further recoding required. It would be more appropriate to refer to these personal identifiers as being 'unique' rather than pseudonymised. The company apologises for this inaccuracy.

c) Please provide a statistical justification for the model chosen for the base case. Please provide any additional analyses that were undertaken and also further analyses that explore additional variables including combinations of (1) varying the 5 cycles to death to 1 cycle (7 days), 3 cycles, 7 cycles and 9 cycles to death identifying which appears to be the best statistically, (2) ECOG 0 at baseline and (3) recurrent disease at baseline, reporting coefficients, s.e. and p values, goodness of fit etc..

Please see response to Question B2a for a discussion of model choice and description of alternative models explored.

As mentioned in Question A1, subgroup data are not available for patients by ECOG PS at

baseline or by recurrent/advanced status.

d) Please provide the arithmetic that causes the values of Appendix D Tables 157 and 158 to lead to the values of Document B Table 64.

Tables 157 and 158 of Appendix P show the regression output from population-averaged panel regression models (specified in STATA v.14.2 using the *XTGEE* function). The equation applied within the Excel model to derive estimated utility index values based on GEE regression output takes the following form:

[redacted]

As an example, the base utility estimate for a patient with progressed disease, within 5 cycles from death ([redacted]), would be calculated as follows:

[redacted]

B2 – Addendum

Please note that the utility values reported in Table 64 in Document B were erroneously calculated for a slightly reduced patient population of N=[redacted], instead of the full GARNET ITT population of patients who responded to the EQ-5D questionnaire (N=[redacted]).

Accordingly, corrected utility values have been calculated for this response. The revised utility values for the N=[redacted] population group are presented in Table 20, Table 21, Table 22 and Table 23, below.

Table 20: GARNET utility values (N=[redacted]) (progression)

	Coefficient	Standard error	P>Z
Baseline utility	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]

Footnote: Values presented to 3dp.

Table 21: GARNET utility values (N=[redacted]) (progression and time to death)

	Coefficient	Standard error	P>Z
Baseline utility	[redacted]	[redacted]	[redacted]
TTD>5 cycles	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]

Footnote: Values presented to 3dp.
Abbreviations: TTD: time-to-death.

Table 22: GARNET health state utility values (N=[redacted]) (progression)

Health state	Estimate
Pre-progression	[redacted]
Progressed disease	[redacted]

Footnote: Values presented to 7dp.

Table 23: GARNET health state utility values (N=[redacted]) (progression and time to death)

Health state	Estimate
Pre-progression >5 cycle from death	[redacted]
Pre-progression ≤5 cycle from death	[redacted]
Post-progression >5 cycle from death	[redacted]
Post-progression ≤5 cycle from death	[redacted]

Footnote: Values presented to 7dp.

Corrected utility values can be found in the Excel file included within the subfolder entitled 'B3. GSK Data on File'. These can be updated in the economic model by doing the following:

- Option 1 GARNET utilities by health state: Updating cells E33:G35 and Q33:T35 on the 'UTILITIES' tab with B11:C13, E11:E13 and B18:D20 in the Excel file included within the subfolder entitled 'B3. GSK Data on File', respectively.
- Option 2 GARNET utilities by health state and time to death: Updating cells E49:G52, Q49:T52 on the 'UTILITIES' tab with B33:C36, E33:E36 and B41:D44 in the Excel file included within the subfolder entitled 'B3. GSK Data on File'.
- Baseline utility value: Update E31:F31 on the 'DASHBOARD' tab with [redacted]

Using the updated utility values, the revised base case results are presented in Table 24 and Table 25.

Table 24: Base case deterministic economic analysis results[a] (dostarlimab list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Current clinical management	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Discounted costs, LYs and QALYs.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life year.

Table 25: Base case deterministic economic analysis results[a] (dostarlimab PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Current clinical management	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,384

Footnotes: [a] Discounted costs, LYs and QALYs.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life year; PAS: patient access scheme.

B3. PRIORITY

Sources of expert elicitation for the dostarlimab NICE appraisal

Clinical expert opinion for the dostarlimab NICE appraisal was sought through an advisory

and subsequent one-to-one meetings with two clinicians. The details of these events are outlined below.

Advisory board

On 26th January 2021, GSK conducted a virtual advisory board with seven clinical experts, including clinical and medical oncologists, gynae-oncology surgeons, a gynaecological histopathologist and a gynaecology clinical nurse specialist, all of whom are involved in the treatment of patients with advanced/recurrent EC in the UK.

The main objectives were to gain insights into the diagnostic testing and management of patients with advanced/recurrent EC in the post-platinum setting in the UK and to obtain specific feedback on the data available for dostarlimab and advice to support the dostarlimab HTA submission.

In advance of the meeting, advisors were asked to familiarise themselves with the recent NICE recommendations on Lynch Syndrome testing in EC (DG42) as well as the ESGO/ESTRO/ESP EC patient management guidelines, and to evaluate if a visual summary of the EC patient journey aligned with their current clinical practice.

The following data were presented during the meeting:

- GARNET trial, Part 2B Cohort A1 (dMMR or MSI-H EC) from the data cut-off of 1st March 2020, including ORR, DOR, OS and PFS efficacy data
- 'Patient towers' estimates of the number of EC patients at various stages of the treatment pathway, based on GSK global market research conducted in 2020 and preliminary RWE research conducted in 2021
- Unpublished KM data followed by modelling extrapolations of GARNET OS and PFS data, alongside matched control data derived from the RWE

Throughout the advisory board, the clinicians were asked a number of polling questions via digital interaction using Slido with multiple choice answers, the results of which were subsequently discussed in the meeting.

Individual one-to-one meetings

Following the advisory board, additional one-to-one teleconference calls were held separately with two of the clinical experts to gain further insights on questions that were unable to be covered during the time of the advisory board. This included seeking further insight into the comparators, including the use of hormone therapy, advice around the subsequent treatment pathway and validation of assumptions in the model concerning time on treatment.

In advance of the meetings, the two clinical experts were sent the questions GSK planned on asking to allow them some time to understand and think through their answers. Following the consultancy, the clinical experts were also asked to answer some more binary questions offline and to return their answers to GSK.

a) Please provide more detail of the elicitation method for the [redacted] proportion of Table 62 together with any GSK data on file report relating

to this, outline the questions posed, the individual responses received and ranges around these individual responses and whether the elicited responses specified [redacted] time point or if this was prespecified during the elicitation exercise.

During the advisory board, the clinicians were shown a chart of the number of patients continuing treatment in the GARNET trial over time, together with extrapolated data estimating approximately [redacted] of patients to be continuing treatment at [redacted]. The advisors were asked "is it appropriate to assume that treatment discontinuation would continue along the same trajectory that we currently see in the figure? This is about [redacted]%".

Five of the seven experts responded "yes" and two responded "no". Of the respondents who disagreed, they considered that the proportion of patients remaining on dostarlimab after [redacted] may be higher than [redacted] if the extrapolated curve flattened, rather than tailing off.

b) Please clarify whether the experts were briefed with the GARNET ToT KM data and the base case fitted curve prior to them responding and whether the implication that their responses would result in something akin to Figure 54 was communicated to them. Please also clarify whether the experts suggested that an absolute [redacted] would remain on treatment from [redacted] onwards or whether 1-[redacted] of people remaining on treatment at [redacted] would discontinue treatment.

As described above in response to B3a, the estimate of [redacted] of patients continuing treatment at [redacted] was presented to the clinicians at the advisory board where five of the seven experts agreed with this assumption. The clinicians at the advisory board indicated that, based on their experience, at least [redacted]% of patients would remain on treatment at [redacted], and during subsequent one-to-one clinician interviews, both clinicians indicated that the proportion of patients on treatment after [redacted] would be between [redacted]%–[redacted]% and would not be higher than [redacted]% after two years.

The attendees were made aware the purpose of the advisory board was in part to seek advice to support the dostarlimab HTA submission and that their responses would be used to inform extrapolation of time-to-event data from GARNET. The clinicians were not shown the Kaplan-Meier curves for ToT or Figure 54 at the advisory board; however, the Kaplan-Meier curves were shown during the subsequent one-to-one clinical validation calls with two clinical experts.

c) If possible, please provide copies of the background briefing and questionnaire, together with an outline of how the elicitation exercise was conducted; e.g. online questionnaire, individual telephone interviews, group meeting.

Please see the overall, initial response to Question B3 for the answer to this request.

d) Please outline any clinical rationale(s) given by the experts that among people in PFS and tolerant of dostarlimab (1) [redacted] would remain on treatment at [redacted] and (2) all people would cease treatment at [redacted]. Please outline the overarching company clinical rationale, i.e. without reference to previous assessments, for these two points in the light of the SmPC.

As described previously in Question 2a and 2b, during two one-to-one clinician interviews, both clinicians indicated that the proportion of patients on treatment after [redacted] would be between [redacted]%–[redacted]% and would not be higher than [redacted]% after [redacted].

Two clinicians were asked about the timepoint at which all patients would discontinue treatment with dostarlimab during one-to-one interviews. One clinician did not provide a specific estimate, and the other clinician estimated they would expect all patients to have discontinued treatment by three years, stating that they "felt that [redacted] was an appropriate amount of time to have a patient on an I-O therapy, and in the absence of a stopping rule, [they] would only expect this to be extended by a small amount and certainly [redacted]".

Considering this, and in line with previously appraised I-O therapies that are recommended alongside a 2-year stopping rule, GSK included a conservative assumption in the base case cost-effective analysis, whereby all patients discontinue treatment with dostarlimab by [redacted] in order to characterise any possible uncertainty about the maximum treatment duration.

e) Has the company elicited any patient/carer involvement around treatment cessation assumptions?

GSK can confirm that no elicitation of patients or carer on treatment cessation was conducted for this appraisal.

B4. It is difficult to align the number of people reported in Table 31 with the GARNET ToT KM values reported in the electronic model ToT worksheet cells AI10:AI54. Please provide an account of how these values are aligned with one another.

The data presented in Table 31 are the raw ToT data analysed directly from the GARNET trial (i.e. not analysed via Kaplan-Meier methodology that differentiates between actual versus censoring events). As such, these data differ from the ToT values included in the electronic model, as these were derived via Kaplan-Meier analyses of the ToT data from GARNET, including differentiation between actual events versus censoring events.

B5. PRIORITY Please confirm that the RWE number of subsequent chemotherapy regimens of Document B 2nd paragraph page 135 was the number of people receiving at least one additional chemotherapy regime subsequent to their 2L chemotherapy regime. Please also provide the

equivalent numerator and denominator restricted to those with an Endometrioid diagnosis. Please state the total number of people in GARNET who had received a subsequent treatment at IA2 and the total number of subsequent treatments received at IA2.

The proportion of patients in the UK RWE GARNET-like cohort who received a subsequent chemotherapy treatment (N=[redacted]; [redacted]%) out of the total number of patients in the UK RWE GARNET-like cohort (N=[redacted]), is referring to patients who received at least one additional regimen subsequent to their 2L chemotherapy regimen. Subgroup data for patients restricted by endometrioid diagnosis are not presented, for the reasons provided in the responses to Questions A1 and A2.

As of IA2, [redacted] patients ([redacted]%) in the GARNET ITT population received a subsequent treatment. In total, [redacted] subsequent treatment regimens were received by the time of IA2 (including radiotherapy [n=[redacted]] and surgery [n=[redacted]]).

B6. The economic model reports a log hazard ratio (HR) for doxorubicin of -2.76 which would appear to imply an HR of 0.10, but an HR of 0.20 is reported. Please provide an account of this.

The company apologises for this inaccuracy in the electronic model. The HR for the individual comparison of PFS for dostarlimab versus doxorubicin based on Makker *et al* (2013)[10] should be HR: [redacted]; 95% CI: [redacted], [redacted]; Log Hazard Ratio = [redacted], p<[redacted], as correctly stated in the Company Submission (Section B3.8.3). To update this, the Log Hazard Ratio should be updated to [redacted] in cell H43 on the 'EFFICACY' tab.

As a result of this change, the corresponding results for Scenarios 35 – 39 and 42 are presented below in Table 26. Note these results also include the update to the utility values as highlighted in the B2 – Addendum.

Table 26: Revised scenario analysis results[a]

No.	Description	List price				With PAS			
		Inc. costs	Incr. QALYs	ICER (£/QALY)	Change versus ICER presented in Document B	Inc. costs	Incr. QALYs	ICER (£/QALY)	Change versus ICER presented in Document B
	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,384	+£163
35	**Individual comparison versus doxorubicin monotherapy based on based on PFS from Makker *et al.* (2013)[10] (HR: [redacted]) and OS from the ZoptEC trial (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£62,781	-£363
36	**Individual comparison versus doxorubicin monotherapy based on PFS from Makker *et al.* (2013)[10] (HR: [redacted];) and OS from McMeekin *et al.* (2015)[11] (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,957	-£327
37	**Individual comparison versus doxorubicin monotherapy based on PFS (HR: [redacted]) and OS from Makker *et al.* (2013)[10] (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,084	-£253
38	**Individual comparison versus doxorubicin monotherapy using PFS from Makker *et al.* (2013)[10] (HR: [redacted]) and OS from Julius *et al.* (2013)[12] (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,191	-£248
39	**Individual comparison versus paclitaxel monotherapy based on PFS from Makker *et al.* (2013)[10] (HR: [redacted]) and OS from McMeekin *et al.* (2015)[11] (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,617	-£294

42	**Individual comparison versus carboplatin monotherapy using doxorubicin monotherapy as a proxy for efficacy: based on PFS from Makker *et al.* (2013)[10] (HR: [redacted]) and OS from the ZoptEC trial (HR: [redacted])**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£65,509	+£142

Footnotes: [a] Discounted costs, LYs and QALYs.

B7. Please tabulate the electronic model settings, with full cell referencing, that are required to generate each of the scenarios of Document B Table 85.

A summary of the electronic model settings required to generate each of the scenarios is presented in Table 27.

Table 27: Electronic model settings required to generate the scenarios presented in Document B, Table 85

Scenario	Description	Required Settings
1	Current clinical management PFS = TTD	Dashboard: Set cell E52 to "TTD"
2	Current clinical management based on ECOG PS ≤1 population	Dashboard: Set cell E47 to "GARNET-like ECOG PS ⩽1 (N=501)"
3	Current clinical management PFS extrapolation = lognormal	Dashboard: Set cell E53 to "Lognormal"
4	Current clinical management OS extrapolation: generalised gamma	Dashboard: Set cell E49 to "Generalised gamma"
5	Current clinical management OS extrapolation: lognormal	Dashboard: Set cell E49 to "lognormal"
6	Current clinical management OS extrapolation based on the application of the HR from the UK RWE MAIC (Scenario 1; HR: [redacted]) to the dostarlimab OS extrapolation	Dashboard: Set cell E48 to "Joint parametric fit" Set cell E50 to "Scenario 1"
7	Current clinical management OS extrapolation based on the application of the HR from the UK RWE MAIC (Scenario 2; HR: [redacted]) to the dostarlimab OS extrapolation	Dashboard: Set cell E48 to "Joint parametric fit" Set cell E50 to "Scenario 2"
8	Current clinical management proportion of patients receiving hormone therapy: 0%	Dashboard: Set cell E46 to "0%"
9	Current clinical management proportion of patients receiving hormone therapy: 10%	Dashboard: Set cell E46 to "10%"
10	Current clinical management proportion of patients receiving hormone therapy: 30%	Dashboard: Set cell E46 to "30%"
11	Current clinical management proportion of patients receiving letrozole: 100%	Costs: Set cell E167 to 0%
12	Dostarlimab PFS extrapolation: Log-logistic	Dashboard: Set cell E43 to "Loglogistic"
13	Dostarlimab PFS extrapolation: Generalised gamma	Dashboard: Set cell E43 to "Generalised gamma"
14	Dostarlimab OS extrapolation: Lognormal (excluding treatment waning)	Dashboard: Set cell E37 to "lognormal" Set cell E72 to "Not applied"
15	Dostarlimab OS extrapolation: Generalised gamma (excluding treatment waning)	Dashboard: Set cell E72 to "Not applied"
16	Time on treatment: loglogistic extrapolation with [redacted]% of patients continuing on treatment	Dashboard: Set cell E65 to "[redacted]%"

	at [redacted] with [redacted]% of patients discontinuing at [redacted]	
17	Time on treatment: loglogistic extrapolation with [redacted]% of patients continuing on treatment at [redacted] with [redacted]% of patients discontinuing at [redacted]	Dashboard: Set cell E66 to "[redacted]"
18	Time on treatment: loglogistic extrapolation with [redacted]% of patients discontinuing treatment at [redacted]	Dashboard: Set cell E66 to "[redacted]"
19	Treatment waning begins at [redacted], [redacted] after [redacted] discontinue treatment with dostarlimab, and is applied for [redacted]	Dashboard: Set cells E74 and E78 to "[redacted]" Set cells E75 and E79 to "[redacted]"
20	Treatment waning begins at [redacted], [redacted] after [redacted] discontinue treatment with dostarlimab, and is applied for [redacted]	Dashboard: Set cells E74 and E78 to "[redacted]" Set cells E75 and E79 to "[redacted]"
21	Treatment waning begins at [redacted], and is applied for [redacted] for PFS and [redacted] for OS	Dashboard: Set cell E75 to "[redacted]" Set cell E79 to "[redacted]"
22	Utility values: GARNET utility values (excluding time-to-death as a covariate)	Dashboard: Set cells E29 and E30 to "GARNET PFS/PD"
23	Utility values: GARNET utility values (excluding age-related utility adjustment)	Dashboard: Set cell E32 to "No"
24	AE disutilities: not included	AEs: Set cells G18–G32 to "0"
25	Diagnostic testing costs: included for all recurrent patients (42%)	Dashboard: Set cell E82 to "Yes"
26	Subsequent therapies source: distribution of subsequent therapies based on those received in GARNET (applied to the GARNET arm only)	Subsequent TX: Set cell E32 to "GARNET distribution"
27	Time horizon: 20 years	Dashboard: Set cell E21 to "20 years"
28	Time horizon: 30 years	Dashboard: Set cell E21 to "30 years"
29	Half-cycle correction: not included	Dashboard: Set cell E22 to "Off"
30	Discount rate costs: 1.5%	Dashboard: Set cell E25 to "1.5%"
31	Discount rate costs: 6%	Dashboard: Set cell E25 to "6.0%"
32	Discount rate outcomes: 1.5%	Dashboard: Set cell E26 to "1.5%"
33	Discount rate outcomes: 6%	Dashboard: Set cell E26 to "6.0%"
34	Discount rate costs and outcomes: 1.5%	Dashboard: Set cells E25 and E26 to "1.5%"

35	Individual comparison versus doxorubicin monotherapy based on based on PFS from Makker *et al.* (2013)[10] (HR: [redacted]) and OS from the ZoptEC trial (HR: [redacted])	Efficacy: Set cell G18 to "ZoptEC IPD analysis (base)" *The result of this scenario is presented on the Results tab, Row 61*
36	Individual comparison versus doxorubicin monotherapy based on PFS from Makker *et al.* (2013)[10] (HR: [redacted];) and OS from McMeekin *et al.* (2015)[11] (HR: [redacted])	Efficacy: Set cell G18 to "MAIC – McMeekin pac/dox" *The result of this scenario is presented on the Results tab, Row 61*
37	Individual comparison versus doxorubicin monotherapy based on PFS (HR: [redacted]) and OS from Makker *et al.* (2013)[10] (HR: [redacted])	Efficacy: Set cell G18 to "MAIC – Makker dox" *The result of this scenario is presented on the Results tab, Row 61*
38	Individual comparison versus doxorubicin monotherapy using PFS from Makker *et al.* (2013)[10] (HR: [redacted]) and OS from Julius *et al.* (2013)[12] (HR: [redacted])	Efficacy: Set cell G18 to "MAIC – Julius pld" *The result of this scenario is presented on the Results tab, Row 61*
39	Individual comparison versus paclitaxel monotherapy based on PFS from Makker *et al.* (2013)[10] (HR: [redacted]) and OS from McMeekin *et al.* (2015)[11] (HR: [redacted])	*No changes required to the base case settings.* *The result of this scenario is presented on the Results tab, Row 62*
40	Individual comparison versus carboplatin plus paclitaxel using PFS (HR: [redacted]) and OS from Rubinstein *et al.* (2019)[13] (HR: [redacted])	Efficacy: Set cells G16 and G17 to "MAIC – Rubinstein carbotaxol" *The result of this scenario is presented on the Results tab, Row 60*
41	Individual comparison versus carboplatin plus paclitaxel using PFS (HR: [redacted],) and OS from Mazgani *et al.* (2008)[14] (HR: [redacted])	Efficacy: Set cells G16 and G17 to "MAIC – Mazgani carbotaxol (both)" *The result of this scenario is presented on the Results tab, Row 60*
42	Individual comparison versus carboplatin monotherapy using doxorubicin monotherapy as a proxy for efficacy: based on PFS from Makker *et al.* (2013)[10] (HR: [redacted]) and OS from the ZoptEC trial (HR: [redacted])	Efficacy: Set cell G14 to "ZoptEC IPD analysis (base)" *The result of this scenario is presented on the Results tab, Row 59*
43	Current clinical management: proportion of patients receiving hormone therapy: 100%	Dashboard: Set cell E46 to "100%"

Abbreviations: AE: adverse events; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; MAIC: matched-adjusted indirect comparison; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; RWE: real-world evidence**.**

B8. Document B Page 137 states: "Additionally, in order to ensure that any OS extrapolations did not provide implausible estimates of mortality, all mortality rates used in the model were bound by the age- and gender-specific natural mortality of the general population as a minimum (calculated using England and Wales life tables [2017–2019]). Adjustments were made in the model traces to ensure that logical inconsistencies, such as the proportion of people alive

being less than the proportion of people alive and progression-free, could not occur (i.e. PFS was bound by OS as a minimum).”

Please specify which of these potential adjustments apply in their base case and which do not apply.

When general population mortality (GPM) exceeded the extrapolated OS, mortality was bound by the age- and gender-specific mortality of the general population. In the dostarlimab arm, OS and GPM converged at [redacted] years when [redacted]% of patients are alive, and in the current clinical management arm they converged at [redacted] years, when [redacted]% of patients are alive. At this point OS was bound by GPM as a minimum; this can be seen in Column S and Column R of the ‘DOSTARLIMAB’ and ‘RWE’ tabs, respectively.

Adjustments were also made to PFS, to ensure the proportion of patients progression-free does not exceed those alive. For dostarlimab, PFS and OS converged at [redacted] years when 0.2% of patients are progression-free, and at 33.0 years in the current clinical management arm, when 0.1% of patients are progression-free. At this point PFS was set equal to OS; this can be seen in Column Y and Column W of the ‘DOSTARLIMAB’ and ‘RWE’ tabs, respectively.

B9. Document B, Section 3.3.7: quote clinicians' opinion on time remaining on dostarlimab treatment: is this a mean of several clinicians' opinions, how many were asked (was it the same six as in the predictions on OS and PFS). It is not clear how this was arrived at and there was no mention of uncertainty around the estimate. Please clarify.

Please see the response to Question B3 for the answer to this question.

Section C: Textual clarification and additional points

Reference pack

NICE and the ERG are aware that the company stated some of the items listed below are “not included within the reference pack as these are either GSK Data on File or not able to be shared”, but wish to request the company to consider sharing them given their importance for the interpretation of findings presented in the company submission.

C1. Please provide the report for the recent advisory board of UK clinicians referred to in the 1st paragraph of B.1.3.6.1, together with any associated background briefing and questionnaire.

The following materials have been provided in the reference pack:

- Pre-reads and presented slides from the advisory board
- Anonymised minutes from the advisory board
- Individual and aggregated poll results from the advisory board

C2. Please provide copies of the data on file references 13, 16, and 54. If the GSK data on file referenced by Document B Tables 53, 56, 58 and 62 is not among these references, please provide this GSK data on file.

The data on file references in Document B Tables 53, 56, 58 and 62 relate to the clinical expert feedback. Details of this are provided in response to Question B3 and the response to Questions C1 and C3.

Reference 13 (GSK Data on File 2021) is referencing the UK RWE study. The UK RWE study report has now been included in the reference pack submitted alongside this response document in the subfolder entitled “C2. GSK Data on File”.

Please see the response to Questions C1 and C3 with regard to Reference 16 (GSK Data on File. Clinical Expert Feedback).

Reference 54 (GARNET Clinical Study Report. July 2019) represents a GARNET clinical study report, pertaining to the previous data cut (July 2019). As agreed on the clarification call with the ERG and NICE on Friday 18th June, that clinical study report does not need to be included in the reference pack. Additional clinical data from the latest March 2020 data cut will be included in response to Question C3 below.

C3. There are three or more unpublished ‘data on file’ documents cited in CS Document B or CS Appendices that cannot be identified in the ‘reference pack’ folders supplied. Please provide all documents referred to (full, unredacted versions):

- **CS Doc B reference number 16. [GSK Data on File]. 2021. Clinical Expert Feedback. Cited on pp 25, 133-134, 141.**

Reference 16 on page 25 relates to estimates for determining the patient population eligible for dostarlimab; these estimates came from the advisory board and relevant materials are provided in the reference pack in response to Question C1.

Reference 16 on pages 133, 134 and 141 relate to the discussions on time-on-treatment and treatment duration assumptions held during the one-to-one clinician interviews, following the advisory board. The relevant slides from those meetings and the anonymised clinician responses to questions related to those slides are provided in the reference pack.

- **CS Appendices reference number 6. [GSK Data on File]. 2021. Cited in many places, including on pp 38, 40, 53, 56, 58, 123-125, 146-152, 154-**

155, 285, 288-292, 294. Text on page 123 refers to different time-points using this same reference number "…and Tables, Listings and Figures (TLFs) from July 2019,6 December 2019 (first data-cut),6 and March 2020 (second data-cut),6 provided by GSK" and CS Appendices Tables 13, 15 and 52 include references to 5, 6, 10-13a with a footnote for a that says "a Three GSK Data on File Tables, Listings and Figures documents were available and included within the SLR.".

Where these have been able to be shared, any data on file relating to the GARNET trial have been included within the reference pack alongside this response document.

- **CS Appendices page 118 says "The programming language for the ZoptEC ITC is provided in the reference pack: 'GSK Data on File (ZoptEC ITC code)'".**

The ZoptEC ITC code has been included within the reference pack accompanying this response.

C4. Please provide the final Statistical Analysis Plan (SAP) for the GARNET study.

The final SAP for GARNET has been included within the reference pack accompanying this response entitled "GSK Data on File. GARNET SAP".

Literature search and study selection

C5. DARE and HTA database are listed in the Information sources in CS Appendices, section D.2, but only CDSR/CENTRAL are mentioned in the top row of tables 6 and 7 and in table 12. Please clarify whether or not these databases were searched and provide numbers for each source.

The DARE and HTA databases were not searched in the clinical SLR, and were erroneously included in the list of databases searched. The company apologies for this discrepancy.

C6. The bibliographic databases Science Citation index (Web of Science) and Conference proceedings Citation Index-Science (CPCI-S) (Web of Science) are listed in information sources in CS Appendices, section D.2, but we don't have search strategies for them. PharmNet.Bund and WHO ICTRP are also listed, but the search strategies and numbers are not provided. Please clarify whether

or not these sources were searched and provide full search strategies with search date, search terms, and numbers for each source.

The Science Citation index (Web of Science), Conference proceedings Citation Index-Science (CPCI-S) (Web of Science), PharmNet.Bund and WHO ICTRP databases and websites were not searched in the clinical SLR, and were erroneously included in the list of sources searched. The company apologies for this discrepancy.

C7. The introduction to the targeted literature review (TLR) for clinical evidence on the efficacy and safety of hormone therapy (Appendix L) reports that Pubmed Central (a full text database) was searched, but later (under 'L.4 Search results'), the much larger database Pubmed is mentioned. Please clarify whether Pubmed Central or Pubmed were searched for the TLR.

The larger PubMed database was searched as part of the hormone therapy TLR.

C8. Cost-effectiveness: please provide a table of excluded references, with full citations and reasons, for the 20 records screened at full-text and excluded in the economic TLR update.

A list of the 20 records screened at the full-text review stage and excluded in the economic TLR update is provided below in Table 28.

Table 28: List of studies excluded at full-text stage in the economic TLR update

	Article	Reason for exclusion
1	Barrington DA, Dilley SE, Smith HJ, Straughn JM Jr. Pembrolizumab in advanced recurrent endometrial cancer: A cost-effectiveness analysis 2019 Gynecol Oncol	Included in original SLR from April/ May 2020
2	Armbruster SD, Previs R, Soliman PT, Westin SN, Fellman B, Jhingran A, Fleming ND. Clinicopathologic features and treatment in patients with early stage uterine clear cell carcinoma: A 16-year experience 2019 Gynecol Oncol	Wrong outcomes
3	Berezowska A, Passchier E, Bleiker E. Professional patient navigation in a hospital setting: a randomized controlled trial 2020 Support Care Cancer	Wrong outcomes
4	Dai S, Nahas S, Murphy JK, Lawrence J, May T, Feigenberg T. Impact and cost of preoperative computed tomography imaging on the management of patients diagnosed with high-grade endometrial cancer 2019 Int J Gynaecol Obstet	Wrong outcomes
5	Klapheke AK, Keegan THM, Ruskin R, Cress RD. Changes in health-related quality of life in older women after diagnosis with gynecologic cancer 2020 Gynecol Oncol	Wrong outcomes
6	Kristeleit, R.; Matthews, C.; Redondo, A.; Huang, J.; Eliason, L.; Im, E.; Brown, J. 858P Patient-reported outcomes (PROs) in the GARNET trial in patients (pts) with advanced or recurrent mismatch repair deficient/microsatelite instability-high (dMMR/MSI-H) endometrial cancer (EC) treated with dostarlimab 2020 Annals of Oncology 31 S637	Wrong outcomes

7	Kumari S. Gynaecologic cancer care during COVID-19 pandemic in India: a social media survey 2020 Cancer Rep (Hoboken)	Wrong outcomes
8	Marth, C et al. ENGOT-en9/LEAP-001: A phase III study of first-line pembrolizumab plus lenvatinib versus chemotherapy in advanced or recurrent endometrial cancer. 2020. Journal of Clinical Oncology. American Society of Clinical Oncology Volume 38	Wrong outcomes
9	Mansoor Raza Mirza, Robert L. Coleman, Lars Christian Hanker, Brian M. Slomovitz, Giorgio Valabrega, Ellie Im, Monica Walker, Wei Guo, Matthew A. Powell ENGOT-EN6/NSGO-RUBY: A phase III, randomized, double-blind, multicenter study of dostarlimab + carboplatin-paclitaxel versus placebo + carboplatin-paclitaxel in recurrent or primary advanced endometrial cancer (EC). 2020	Wrong outcomes
10	Matei D, Filiaci V, Randall ME, Mutch D, Steinhoff MM, DiSilvestro PA, Moxley KM, Kim YM, Powell MA, O'Malley DM, Spirtos NM, Small W Jr, Tewari KS, Richards WE, Nakayama J, Matulonis UA, Huang HQ, Miller DS. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer 2019 N Engl J Med[15]	Wrong outcomes
11	Mileshkin L, Edmondson R, O'Connell RL, Sjoquist KM, Andrews J, Jyothirmayi R, Beale P, Bonaventura T, Goh J, Hall M, Clamp A, Green J, Lord R, Amant F, Alexander L, Carty K, Paul J, Scurry J, Millan D, Nottley S, Friedlander M; PARAGON study group. Phase 2 study of anastrozole in recurrent estrogen (ER)/progesterone (PR) positive endometrial cancer: The PARAGON trial - ANZGOG 0903 2019 Gynecol Oncol	Wrong outcomes
12	Riedinger CJ, Kimball KJ, Kilgore LC, Bell CW, Heidel RE, Boone JD. Water only fasting and its effect on chemotherapy administration in gynecologic malignancies 2020 Gynecol Oncol	Wrong outcomes
13	Thaker NG, Holloway J, Hodapp C, Mellen M, Fryefield D, Meghani R, Tong K, Rose CM. Automated Big Data Analytics for the Radiation Oncology Alternative Payment Model Proposal Using a Novel Health Care Software Technology 2020 JCO Oncol Pract	Wrong outcomes
14	Coleridge S, Morrison J. Patient-initiated follow-up after treatment for low risk endometrial cancer: a prospective audit of outcomes and cost benefits 2020 Int J Gynecol Cancer	Wrong population
15	Ferrari F, Forte S, Sbalzer N, Zizioli V, Mauri M, Maggi C, Sartori E, Odicino F. Validation of an enhanced recovery after surgery protocol in gynecologic surgery: an Italian randomized study 2020 Am J Obstet Gynecol	Wrong population
16	Jin M, Hou X, Sun X, Zhang Y, Hu K, Zhang F. Impact of different adjuvant radiotherapy modalities on women with early-stage intermediate- to high-risk endometrial cancer 2019 Int J Gynecol Cancer	Wrong population
17	Ngu SF, Wei N, Li J, Chu MMY, Tse KY, Ngan HYS, Chan KKL. Nurse-led follow-up in survivorship care of gynaecological malignancies-A randomised controlled trial 2020 Eur J Cancer Care (Engl)	Wrong population
18	Papathemelis T, Scharl S, Hipp M, Scharl A, Beckmann MW, Lux MP, Kölbl O. Quality of life and oncological outcome in endometrial cancer patients after vaginal brachytherapy: comparison of two dosing schemes 2019 Arch Gynecol Obstet	Wrong population
19	Tsubamoto H, Ueda T, Inoue K, Isono-Nakata R, Saeki S, Kato Y, Shibahara H. Effects of leuprorelin for the treatment of recurrent	Wrong population

	gynecological cancer by assessment including self-administered quality-of-life questionnaire 2019 J Obstet Gynaecol Res	
20	Zandbergen N, de Rooij BH, Vos MC, Pijnenborg JMA, Boll D, Kruitwagen RFPM, van de Poll-Franse LV, Ezendam NPM. Changes in health-related quality of life among gynecologic cancer survivors during the two years after initial treatment: a longitudinal analysis 2019 Acta Oncol	Wrong population

Abbreviations: TLR: targeted literature review.

References

1. Phillippo DM, Ades, A.E., Dias, S., Palmer, S., Abrams, K.R., Welton, N.J.,. National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD) 18: Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE. Available at: http://nicedsu.org.uk/technical-support-documents/population-adjusted-indirect-comparisons-maic-and-stc/ [accessed 27 April 2021].
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6. [GSK Data on File]. 2021.
7. ClinicalTrials.gov. Zoptarelin doxorubicin (AEZS 108) as second line therapy for endometrial cancer (ZoptEC). Available at: https://clinicaltrials.gov/ct2/show/NCT01767155 [accessed 23 June 2021]. Volume 2020.
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13. Rubinstein M, Halpenny D, Makker V, et al. Retreatment with carboplatin and paclitaxel for recurrent endometrial cancer: A retrospective study of the Memorial Sloan Kettering Cancer Center experience. Gynecol Oncol Rep 2019;28:120-123.

14. Mazgani M, Le N, Hoskins PJ. Reuse of carboplatin and paclitaxel in patients with relapsed endometrial cancer--the British Columbia Cancer Agency experience. Gynecol Oncol 2008;111:474-7.
15. Matei D, Filiaci V, Randall ME, et al. Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer. New England Journal of Medicine 2019;380:2317-2326.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Endometrial cancer (advanced, recurrent, high microsatellite instability, mismatch repair deficiency, treated) - dostarlimab [ID3802]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Cathryn Edwards**
2. Name of organisation	**NCRI-ACP-RCP-RCR**

3. Job title or position	**RCP registrar**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**National Cancer Research Institute – nationally funded research organisation**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Executive summary	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts the key messages of our submission are as follows: • Group of patients with limited current standard of care options • Immunotherapy - Novel treatment option – • Durable responses and manageable side effect profile • Dostarlimab is also being evaluated in combination with carboplatin and paclitaxel in patients with primary advanced or recurrent endometrial cancer in the phase 3 RUBY (NCT03981796) trial.
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	The main aim of treatment is to improve progression free survival and to control symptoms by reducing tumour bulk (inducing a clinical response).

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinically significant treatment responses can be subjective (improvement in patient symptoms) and objective (response by imaging), and in this setting although >30% response is deemed significant by RECIST, stable disease by RECIST is still a clinically important endpoint in terms of symptom benefit. Furthermore standard RECIST criteria may underestimate the clinical benefit of immunotherapies and to account for this irRECIST (immune related RECIST) by investigator assessment was a prespecified secondary endpoint in the GARNET trial, - there were not significant differences seen compared to RECIST and so clinically either could be used to assess response.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Women with relapsed /advanced endometrial cancer have limited efficacious treatment options open to them and so novel therapeutic options are a significant need in this group of women.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Endometrial cancer (EC) is the most common gynecologic malignancy in the US and European Union. While many patients are diagnosed with early stage disease (FIGO stage I and II) that is often curable with surgery with or without adjuvant treatment, about 20 % of these patients experience disease relapse, and 25-30 % of women present with FIGO stage III-IV disease. Overall mortality rates have increased by more than 20 % since 1990 and there were almost 2000 deaths from endometrial cancer in the UK in 2011 (Cancer Research UK CancerStats 2014). EC has demonstrated the highest rates of mismatch mutation repair–deficient (dMMR) and microsatellite instability–high (MSI-H) tumors among all tumors (approximately 30%)

	Currently women with advanced endometrial cancer will receive combination chemotherapy (generally carboplatin and taxol) and some may require targeted radiotherapy for symptom control (e.g bone mets). First line treatment of advanced endometrial cancer - multiple phase II trials have shown that, despite response rates of 50-60 % with carboplatin-paclitaxel, median overall survival (OS) is disappointing (median of 15-18 months). Those women with recurrent endometrial cancer have limited treatment options – either systemic chemotherapy or a clinical trial if fit. No defined standard for second-line therapy exists, and phase II evaluations of multiple cytotoxic agents have reported response rates in this setting of approximately 10 % with median PFS and OS of 3 and 10 months respectively (Fleming et al 2015). There is therefore an urgent need to define more effective treatment strategies for recurrent/ progressive endometrial cancer. In the absence of a defined second-line or later standard treatment, many centres are utilising weekly paclitaxel in this setting as it is well-tolerated, has little negative impact on quality of life and is supported by phase II data (Homesley et al 2008) documenting a 27 % response rate.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	• Guidelines are routinely used to guide treatment: ESMO • BGCS • ESGO/ESTRO/ESP guidelines for the management of endometrial cancer
• Is the pathway of care well defined? Does it vary or are there differences of opinion	The pathway of care is well defined and generally follows the guidelines referred to above. Nationally there may be differences in terms of funding various agents such as weekly taxol, access to clinical trials and, until recent NICE guidance, to the availability of routine MMR testing.

between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	This would be an important step forward in offering a targeted and efficacious treatment option for women with difficult to treat advanced/relapsed disease, where limited treatment options exist currently
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The recommendation would be for dostarlimab to be used in women with dMMR (detected by immune histochemistry (IHC), as per the results of the GARNET trial, - as this was the group who had the highest response rate to treatment.
• How does healthcare resource use differ between the technology and current care?	Currently in the relapsed setting weekly intravenous chemotherapy with paclitaxel is generally the most routinely used treatment. If dostarlimab were to be used in this setting then there would be fewer potential IV treatment slots required as the regimen for dostarlimab is 500 mg of intravenous (IV) every 3 weeks for 4 cycles followed by 1000 mg IV every 6 weeks until disease progression.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This would be run via specialist clinics – Oncology- but could be run by advanced nurse practitioners/ non medical prescribers with medical oversight.
• What investment is needed to introduce the technology? (For	Immunotherapy with PD1/PD L1 inhibitors is well established in the treatment of a number of solid tumours and all cancer centres/units are well set up to prescribe/ deliver/ deal with side effects of treatment. No additional facilities/equipment or training are likely to be required.

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes - Dostarlimab, a PD-1 inhibitor, recently demonstrated clinical activity in patients with dMMR and MMR proficient (MMRp) endometrial cancer. The approval of dostarlimab has the potential to change the way we treat dMMR advanced or recurrent endometrial cancer after standard platinum-based chemotherapy, especially given the overall response rate and durability of response that was seen in the GARNET trial: The dMMR endometrial cancer cohort of the multicenter, single-arm, multiple parallel-cohort, open-label GARNET study, dostarlimab elicited a 42.3% objective response rate (ORR) in 71 patients with dMMR recurrent or advanced endometrial cancer. This included a 12.7% complete response (CR) rate and a 29.6% partial response (PR) rate. The duration of response (DOR) was at least 6 months for 93.3% of responders, and the median DOR was not reached at a median follow-up of 14.1 months (2.6-22.4+). Dostarlimab has been approved under the FDA's Real-Time Oncology Review pilot program and in February 2021, the European Medicines Agency's Committee for Medicinal Products for Human Use granted a positive opinion to dostarlimab as a treatment for patients with recurrent or advanced microsatellite instability–high/dMMR endometrial cancer who have progressed on or following platinum-based chemotherapy.
• Do you expect the technology to increase length of life more than current care?	Based on the results (detailed below) of the GARNET trial we expect dostarlimab to have a significant impact on progression free survival compared to current care. GARNET (NCT02715284) was a phase 1, single-arm study of dostarlimab (TSR-042) monotherapy in multiple tumor types In part 2B, 126 patients with dMMR EC and 145 patients with MMRp EC were enrolled; dostarlimab was dosed at the recommended therapeutic dose determined from parts 1 and 2A: 500 mg IV every 3 weeks for 4 cycles, then 1000 mg IV every 6 weeks until disease progression. MMR status was determined by immunohistochemistry (IHC). Primary endpoint: ORR and DOR

	Dostarlimab elicited a irORR of 45.5% in patients with dMMR EC, and 13.9% in patients with MMRp.This included a 12.7% complete response (CR) rate and a 29.6% partial response (PR) rate. The duration of response (DOR) was at least 6 months for 93.3% of responders, and the median DOR was not reached at a median follow-up of 14.1 months (2.6-22.4+). Additional results revealed that the investigator-assessed immune RECIST (irRECIST) disease control rate (DCR) was 63.6% in the dMMR cohort vs 42.4% in the MMRp cohort. Dostarlimab also demonstrated a disease control rate of 35.2%–2.1% CR, 11.3% PR, 21.8% SD–in patients with MMRp EC; this patient population was comprised of a higher percentage of patients with Type II EC, which is historically associated with a worse prognosis . The BICR-assessed DCRs by RECIST v1.1 criteria were 57.3% and 35.2%, respectively This is a significant improvement compared to standard therapies where phase II evaluations of multiple cytotoxic agents have reported response rates in this setting of approximately 10 % with median PFS and OS of 3 and 10 months respectively (Fleming et al 2015).
• Do you expect the technology to increase health-related quality of life more than current care?	Yes by controlling symptoms we would expect an improvement in quality of life. The agent was well tolerated in the GARNET trial : among 104 patients evaluable for safety, the most common (≥20%) adverse events (AEs) included fatigue (48%), nausea (30%), diarrhoea (26%), anaemia (24%), and constipation (20%). The most common (≥2%) grade 3/4 AEs included anaemia and increase in alanine transaminase levels. There were a small number of patient discontinuations of dostarlimab due to AEs occurred in 5 (4.8%) of patients, and no drug-related deaths occurred.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This agent has shown benefit in the patients with dMMR and MMR proficient (MMRp) endometrial cancer, in the phase 1 GARNET (NCT02715284) trial. However the magnitude of benefit was greater in the dMMR group and this subgroup of patients would be the group we recommend approval of dostarlimab.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	All centres will need some initial time to become familiar with the use of dostarlimab, but no significant concerns are anticipated with the use of this agent. The majority of centres/cancer units are familiar with the use of PD1/PD L1 inhibitors in a number of solid tumours and are therefore well versed in dealing with delivery and also side effects of immunotherapy.; and also have established relationships with other specialties , which is essential when treating with immunotherapy (eg endocrine/GI etc).

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The standard stopping rules for immunotherapy will be utilised- clinically significant progression requiring a change of treatment or unacceptable toxicity. No additional testing is required.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	The approval of dostarlimab has the potential to change the way we treat dMMR advanced or recurrent endometrial cancer after standard platinum-based chemotherapy, especially given the overall response rate and durability of response that was seen in the GARNET trial

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	This is a significant step change for the treatment of relapsed dMMR advanced/relapsed endometrial cancer- for the reasons discussed in section 11.
• Does the use of the technology address any particular unmet need of the patient population?	Yes- this is a population where no standard therapy currently exists.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The adverse events associated with dostarlimab are expected with this class of agents and can be monitored for during treatment to minimise impact on patient quality of life.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	yes

• If not, how could the results be extrapolated to the UK setting?	The population in the GARNET trial is applicable to the UK population
• What, in your view, are the most important outcomes, and were they measured in the trials?	The trials have appropriately investigated the activity (overall response rates/ duration of response) and safety/side effects (toxicity) of dostarlimab. The GARNET trial evaluated single agent dostarlimab in multiple tumour types followed by an expansion phase in cohort included 5 groups: dMMR endometrial cancer (A1; n = 129), MMRp endometrial cancer (A2; n = 161), non–small cell lung cancer (E), nonendometrial dMMR/MSI-H cancer (F), and platinum-resistant ovarian cancer (G).
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	N/A
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NO

20. How do data on real-world experience compare with the trial data?	NA
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	None known
21b. Consider whether these issues are different from issues with current care and why.	NA
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Group of patients with limited current standard of care options
- Immunotherapy - Novel treatment option –
- Durable responses and manageable side effect profile
- Dostarlimab is also being evaluated in combination with carboplatin and paclitaxel in patients with primary advanced or recurrent endometrial cancer in the phase 3 RUBY (NCT03981796) trial.

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Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]

Produced by	*Warwick Evidence*
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Declared competing interests of the authors
Prof Emma Crosbie is Trustee of Peaches Womb Cancer Trust, which educates, raises awareness and supports survivors of endometrial cancer through social media, learning events and research. She served on a virtual endometrial cancer advisory board (not specifically convened for dostarlimab and the current appraisal) organised by GSK in June 2020 and was paid for her time. All other authors declare that they have no competing interests.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Toyin Lamina (Independent Researcher) led and Amin Mehrabian (Independent Researcher) supported the critique of clinical effectiveness evidence; Ewen Cummins (Partner/Senior Researcher) and Rhona Johnston (Computer Modeller), supported by Martin Connock (Honorary Senior Research Fellow), reviewed and critiqued the cost-effectiveness evidence and the company model and undertook additional analyses; Paul Coleman (Public Health Specialty Registrar) provided clinical summary and critique of clinical effectiveness evidence and end of life criteria; Rachel Court (Information Specialist) critiqued the company searches and undertook additional searches Yen-Fu Chen (Associate Professor) critiqued the decision problem and indirect comparisons, co-ordinated the project and the report; Emma Crosbie (Professor and Honorary Consultant) provided expert clinical advice and critical comments. All authors contributed towards and commented on drafts of this report and approved the final report.

Please note that: Sections highlighted in [redacted] are '[redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue.

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Abbreviations

AE	Adverse event
AUC	Arena under the curve
BGCS	British Gynaecological Cancer Society
BICR	Blinded independent central review
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
BSC	Best standard of care
CASP	Critical Appraisal Skills Programme
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use

CI	Confidence interval
CR	Complete response
CS	Company submission. Unless otherwise specified, CS section numbers, tables and figures cited in this ERG report refer to those of Document B of the company submission.
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle X Day X
DCO	Data cut off
DCR	Disease control rate
DG	Diagnostics guidance
dMMR	DNA mismatch repair deficient
DOR	Duration of response
DOST	Dostarlimab
DSA	Deterministic sensitivity analysis
DSU	Decision support unit
EC	Endometrial cancer
ECOG PS	Eastern Cooperative Oncology Group performance score
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EORTC QLQ-C3-	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	End-of-treatment
EPAR	European Public Assessment Report
EQ-5D	EuroQoL 5-dimensions 5-levels
ESGO	European Society of Gynecological Oncology
ESMO	European Society for Medical Oncology Annual Meeting

ESP	European Society of Pathology
ESS	Effective sample size
ESTRO	European Society for Radiotherapy and Oncology
FIGO	International Federation of Gynaecology and Obstetrics
HR	Hazard ratio
HR+	Hormone receptor positive
HRQoL	Health-related quality of life
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
I-O	Immuno-oncology
IPD	Individual patient data
IPTW	Inverse probability treatment weighting
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan-Meier
LYG	Life-years gained
MAIC	Matching-adjusted indirect comparison
MHRA	Medicines & Healthcare products Regulatory Agency
MMR	DNA mismatch repair
MSI-H	Microsatellite instability-high
MSS	Microsatellite stable
NCRAS	National Cancer Registry Analysis System
NHS(E)	National Health Service (England)
NNT	Numbers needed to test

NR	Not reported
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PD-L1/2	Programmed death-ligand 1/2
PFS	Progression-free survival
PH	Proportional hazards
PLD	Pegylated liposomal doxorubicin
pMMR	DNA mismatch repair proficient
PPS	Post-progression survival
PR	Partial response
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QXW	Once every X weeks
QALY	Quality-adjusted life-years
QOL	Quality of life
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
RWE	Real-world evidence
RWEQ	Real World Evidence Equivalent dataset. This abbreviation is adopted in this report as a more concise way to refer to the main

	comparator patient population/dataset chosen by the company, the GARNET-like Real World Evidence dataset (n=[redacted])
SACT	Systemic Anti-Cancer Therapy (SACT) dataset
SAE	Serious adverse event
SD	Stable disease
SLR	Systematic literature review
STC	Simulated treatment comparisons
STD	Standard deviation
TEAE	Treatment emergent adverse event
ToT	Time on treatment
TTD	Time to discontinuation
TTNT	Time to next treatment
VAS	Visual analogue scale

Executive Summary

1 Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 *Overview of the ERG's key issues*

Table 1: Summary of key issues

Issues	Summary of issue	Report sections
Issue 1	The patient population specified in marketing authorisation and addressed in the company submission (CS) is narrower that what is specified in the final scope	2.3
Issue 2	Patients with advanced disease and with recurrent disease are potentially two distinct populations, but they were identified in different ways between the GARNET trial for dostarlimab and the GARNET-like Real World EQuivalent (RWEQ) cohort	2.3 & 3.3.1.1
Issue 3	Overall the GARNET trial data were fairly immature and may not be sufficient to provide reliable effectiveness and cost-effectiveness estimates	3.2
Issue 4	There are uncertainties over the magnitude of the benefit of dostarlimab relative to comparators due to the single-arm design of the GARNET trial and lack of suitable data for comparator treatments	3.3
Issue 5	GARNET trial population and RWEQ cohort may have fundamental differences that cannot be easily adjusted statistically	3.3.1

Issues	Summary of issue	Report sections
Issue 6	Does the model contain a number of errors, in particular with regards to the waning of the dostarlimab treatment effect after cessation of treatment?	4.3.1
Issue 7	Is the company elicitation exercise for dostarlimab overall survival (OS) mainly relevant to the curves unadjusted for treatment waning, and what does this imply for the choice of the adjusted OS curve?	4.2.6.5 4.3.3.2
Issue 8	Does the company elicitation exercise for current treatment OS suggest that the RWEQ OS data and curves are too pessimistic?	4.2.6.3
Issue 9	Is the company elicitation exercise for dostarlimab treatment discontinuation and waning of treatment effect biased, and if so what does this imply for the values that should be applied?	4.3.3.3
Issue 10	Is the company choice of dostarlimab time to treatment discontinuation (TTD) curve appropriate or would the better fitting Gompertz have been the more natural choice? Is the ERG estimated intention to treat (ITT) TTD generalized gamma a better choice?	4.3.3.8
Issue 11	GARNET had a lot of censoring, quite a lot of which was early censoring. The RWEQ data has much less censoring. Might poorly performing patients have dropped out of GARNET early and if they did how might this have affected results?	4.3.3.5
Issue 12	For the ICERs for dostarlimab compared to individual treatments, does the difference in effect when using RWEQ data compared to when using values within the literature raise questions about the reliability of using the RWEQ data?	4.3.3.6 5.2 6.2

A key difference between the company's preferred assumptions and the ERG's preferred assumptions is whether there are errors in the model implementation. The ERG reports the company base case ICER of £37,311[1] per quality adjusted life year (QALY), but for most of its commentary of Chapter 4 it references the ERG corrected company base case ICER of £49,190 per QALY.

The other main differences between the company and the ERG are:

[1] Updated for the revised PAS of [redacted] presented during technical engagement rather than the [redacted] of the original company submission.

- Should overall survival for dostarlimab be modelled using the generalised gamma or the Weibull?
- Should the dostarlimab time to treatment discontinuation be modelled using the company log-logistic, the company Gompertz or the ERG ITT generalised gamma?
- Is it most reasonable that all but [redacted] of dostarlimab patients will cease or have treatment withdrawn at the [redacted] point, or is [redacted] more reasonable? Would a treatment withdrawal cliff edge be applied in practice?
- When patients have dostarlimab treatment withdrawn, is it reasonable to assume that the full benefits of treatment will be retained for [redacted] or is it more reasonable to assume that there will be some loss of effect, albeit small, from when treatment is withdrawn?

1.2 *Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained.

The company estimates the effects of current treatment and dostarlimab as per Table 3, with an [redacted] corresponding central estimate from the probabilistic modelling is £35,492 per QALY.

Table 2: Summary of the company base case

	Current treatment	Dostarlimab	Net
Life years QALYs Costs	[redacted]	[redacted]	[redacted]
ICER			£37,311

Note that the life years reported above are undiscounted, while QALYs and costs are discounted at 3.5%. The ERG applies this convention throughout this report.

Further note that during clarification the company supplied an updated base case due to a slight expansion of the quality of life data set that very slightly worsens its base case, together with a corresponding set of scenario analyses. The ERG has not incorporated these in its report due to time constraints. The ERG thinks the revision

is sufficiently minor to be unlikely to affect Committee deliberations. The ERG revised base case incorporates the change to the quality of life data set.

The company univariate sensitivity analyses find that the ICER is most sensitive to: the baseline quality of life, the quality of life for the main health states of the model and the cost per cycle of dostarlimab.

The company performs a number of comparisons with individual treatments using hazard ratios derived from the company's MAICs based on comparator effectiveness data from the literature.

[redacted]

1.3 *The decision problem: summary of the ERG's key issues*

Issue 1: The patient population specified in marketing authorisation and addressed in the company submission (CS) is narrower that what is specified in the final scope

Report section	2.3
Description of issue and why the ERG has identified it as important	The population specified in marketing authorisation and addressed in the CS is required to "have progressed on or following prior treatment with a platinum-containing regimen" rather than simply "previously treated" endometrial cancer (EC) as described in the final scope.
What alternative approach has the ERG suggested?	No alternative approach is required. CS highlighted this difference and ERG critiqued and interpreted the submitted evidence accordingly.
What is the expected effect on the cost-effectiveness estimates?	This issue impacts on applicability (generalisability) of clinical effectiveness and cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence or analyses are required. This issue is flagged up to highlight the specific patient population to which the evidence submitted by the company and critiqued by the ERG can be applied.

Issue 2: Patients with advanced disease and with recurrent disease are potentially two distinct populations, but they were identified in different ways between the GARNET trial for dostarlimab and the GARNET-like Real World Evidence equivalent (RWEQ) cohort

Report section	2.3 & 3.3.1.1
Description of issue and why the ERG has identified it as important	The nature of tumour, and hence prognosis, may differ between patients with advanced disease and those with recurrent disease. These two groups of patients also have different treatment histories, which may impact on the response to treatment. While recurrent disease in the GARNET trial was confirmed by radiographic evidence, 'probable' recurrent disease could only be retrospectively identified based on treatment history without supporting radiographic evidence in the GARNET-like real-world evidence equivalent (RWEQ) cohort (which is the main comparator chosen by the company) due to limitations in registry data. This difference may impact on the comparability of patients between GARNET and RWEQ, and may confound the comparison between treatments.
What alternative approach has the ERG suggested?	ERG requested data stratified by advanced vs recurrent disease for both the GARNET and the RWEQ cohorts in ERG's clarification questions. However the company did not provide data for either cohort. The company explained that recurrent and advanced diseases were mentioned in the same inclusion criterion and were not recorded separately in the GARNET trial, and stated that "further subgroup analyses of the licensed dostarlimab indication were not included in the NICE final scope and should not be considered relevant to this appraisal" (company response to ERG clarification question A2).
What is the expected effect on the cost-effectiveness estimates?	The direction and magnitude of the expected effect is not clear, but potential differences in the characteristics and composition between the two cohorts with respect to advanced vs recurrent diseases may confound clinical effectiveness estimates and directly impact on cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Although recurrent and advanced diseases were not separately recorded in the GARNET trial, it should be possible to adopt the same definition of advanced disease being FIGO stage III & IV at diagnosis (or at treatment initiation) and then classify remaining patient groups as recurrent. Comparison between GARNET and RWEQ can then be carried out between the better defined 'advanced disease' groups and the less well-characterised 'recurrent disease' groups (which were defined and identified in different ways) to verify the sources of heterogeneity in the patient characteristics observed between the two cohorts and to explore whether these might have a bearing on observed outcomes.

1.4 *The clinical effectiveness evidence: summary of the ERG's key issues*

Issue 3: Overall the GARNET trial data were fairly immature and may not be sufficient to provide reliable effectiveness and cost-effectiveness estimates

Report section	3.2
Description of issue and why the ERG has identified it as important	With a medium duration of follow up of [redacted] months and median overall survival time not yet reached, the key effectiveness data for dostarlimab were immature and longer-term effectiveness unknown.
What alternative approach has the ERG suggested?	No alternative seems to be possible within the current appraisal.
What is the expected effect on the cost-effectiveness estimates?	The substantial uncertainties in longer-term effectiveness directly contribute to substantial uncertainties in cos-effectiveness estimates
What additional evidence or analyses might help to resolve this key issue?	Data from longer follow-up might resolve this issue. The committee might consider the option for use within the Cancer Drug Fund while longer-term data are accrued to reduce uncertainties.

Issue 4: There are uncertainties over the magnitude of the benefit of dostarlimab relative to comparators due to the single-arm design of the GARNET trial and lack of suitable data for comparator treatments

Report section	3.1, 3.2 and 3.4
Description of issue and why the ERG has identified it as important	GARNET was a single arm, phase I trial with no comparator. Relative effectiveness needs to be estimated through unanchored indirect comparison. The company made substantial effort in identifying different sources of comparator evidence and undertook a series of matching adjusted indirect comparisons (MAICs), but all of the MAICs were susceptible to bias due to limitations in available data and methods of MAICs.
What alternative approach has the ERG suggested?	Improving some of the MAICs may reduce potential bias (see further Key issues below) but may not eliminate residual confounding, the direction and magnitude of which is difficult to estimate.
What is the expected effect on the cost-effectiveness estimates?	The expected impact on the cost-effectiveness estimates varies depending on individual comparators and MAICs, but may be difficult to estimate because of confounding by indication for different comparators.
What additional evidence or analyses might help to resolve this key issue?	Data on real world use of dostarlimab, possibly collected from a randomized controlled trial (RCT) of dostarlimab versus current clinical management may be needed.

Issue 5: GARNET trial population and RWEQ may have fundamental differences that cannot be easily adjusted statistically

Report section	3.3.1
Description of issue and why the ERG has identified it as important	There are uncertainties around the process used to derive the GARNET-like Real World Evidence equivalent (RWEQ) cohort from the patients with EC diagnosis in the registry and the representation of the UK population. There are major differences in setting, patient characteristics and case definitions between the GARNET trial population and the RWEQ cohort, which was chosen by the company as the main comparator for the base case. There is uncertainty regarding the approaches the company undertook to align the data. The MAIC conducted by the company for GARNET vs RWEQ did not take into account some important prognostic factors and had many methodological issues. There are reservations regarding the validity of the findings from the MAICs.
What alternative approach has the ERG suggested?	In order to characterise the differences between GARNET and RWEQ and to identify potentially more comparable patients between the cohorts, ERG requested data stratified by advanced vs recurrent diseases, and by endometrioid vs other diseases for both cohorts in ERG's clarification questions. However, no data were provided.
What is the expected effect on the cost-effectiveness estimates?	The differences between GARNET and RWEQ are likely to result in effectiveness and cost-effectiveness estimates that are biased in favour of dostarlimab.
What additional evidence or analyses might help to resolve this key issue?	The following analyses may reduce the magnitude of potential bias: • Examination of RWEQ patients with known mismatch repair deficiency (dMMR) status at the time of diagnosis to compare similar tumour biology. • Analyses focusing on more homogeneous groups of patients, e.g. endometrioid disease or advanced disease (which could be operationally defined as International Federation of Gynaecology and Obstetrics [FIGO] stage III and IV). • Comparison of GARNET with subset(s) of patients receiving combination regimens in the RWEQ who might represent fitter patients similar to those recruited in trial settings. • Consider the use alternative sources of more comparable data (such as ZoptEC trial) as primary analyses for base case.

1.5 *The cost-effectiveness evidence: summary of the ERG's key issues*

Issue 6: Model errors

Report section	4.3.1
Description of issue and why the ERG has identified it as important	There appear to be modelling errors, particularly the implementation of the waning of treatment effect.
What alternative approach has the ERG suggested?	The company applies hazard ratios. But the RWEQ curves of the base case are based upon the RWEQ parameterised curves. Equalising the risk of events between the arms requires that the risk of events in the RWEQ arm be used. There are a number of other more minor modelling errors.
What is the expected effect on the cost-effectiveness estimates?	The company base case ICER of £37,311 per QALY worsens to £49,190 per QALY. Given the importance of this, the ERG thinks that the £37,311 ICER is no longer relevant. For the ERG critique of Chapter 4 the ERG presents the effects that its other changes have upon the ERG corrected company base case ICER of £49,190 per QALY.
What additional evidence or analyses might help to resolve this key issue?	None.

Issue 7: Dostarlimab overall survival (OS) elicitation exercise and choice of OS curve

Report section	4.2.6.5 & 4.3.3.2
Description of issue and why the ERG has identified it as important	The elicitation exercise concentrated upon the unadjusted curves. The ERG thinks that this means it provides values for the unadjusted curves but it is not a good basis for selecting the adjusted curves.
What alternative approach has the ERG suggested?	The ERG prefers the company OS Weibull over the company OS log-logistic.
What is the expected effect on the cost-effectiveness estimates?	This worsens the ERG corrected company base case ICER from £41,190 per QALY to £65,262 per QALY.
What additional evidence or analyses might help to resolve this key issue?	None.

Issue 8: RWEQ OS elicitation exercise and choice of OS curve

Report section	4.2.6.3
Description of issue and why the ERG has identified it as important	The company sponsored experts were also asked about OS at 5, 10 and 15 years under current therapy. Their responses suggest that the curves fitted to the RWEQ data extrapolate too low an OS at 5, 10 and 15 years. The RWEQ data may be poorly aligned with the GARNET population. The OS for the individual treatments within the RWEQ are also hugely different from one another, those receiving combination therapies performing much better than those receiving monotherapies. Aggregating the RWEQ patients into a single treatment groups may not be sensible.
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	If the RWEQ OS underestimates what OS is with current therapy the ICER is biased in favour of dostarlimab.
What additional evidence or analyses might help to resolve this key issue?	GARNET and RWEQ baseline and KM data split by endometrioid disease, Eastern Cooperative Oncology Group (ECOG) performance status and if possible recurrent disease status, possibly drilling down into individual treatments as well.

Issue 9: Dostarlimab time to treatment discontinuation (TTD) elicitation exercise and treatment discontinuations

Report section	4.3.3.3
Description of issue and why the ERG has identified it as important	The elicitation exercise appears to have presented the TTD numbers remaining at risk rather than the TTD KM survival curve. If so, this would seriously bias the presentation. The company sponsored experts were not asked open ended questions but in the main were asked to confirm the company preferences. The company does not present evidence that there will be no loss of effect for any patients for [redacted] after treatment cessation. The ERG thinks that the TTD elicitation exercise is probably biased and at best yields a floor for the treatment cessation percentage. The ERG also thinks that it is more reasonable to assume that some, albeit small, treatment waning will start from treatment cessation.
What alternative approach has the ERG suggested?	The ERG assumes that at [redacted] the proportion remaining on treatment will fall to [redacted], treatment waning will occur over the next [redacted] and all will cease treatment at [redacted].
What is the expected effect on the cost-effectiveness estimates?	This worsens the ERG corrected company base case ICER from £49,190 per QALY to £60,362 per QALY.
What additional evidence or analyses might help to resolve this key issue?	None.

Issue 10: Dostarlimab choice of TTD curve

Report section	4.3.3.8
Description of issue and why the ERG has identified it as important	The company selected the company log-logistic but the company Gompertz has superior information criteria. Due to the treatment cessation assumptions, the dostarlimab TTD curve does not require much extrapolation. The choice of curve can be based upon the internal goodness of fit.
What alternative approach has the ERG suggested?	The ERG prefers the company Gompertz over the company log-logistic due to its better information criteria. The ERG prefers the ERG ITT generalized gamma.
What is the expected effect on the cost-effectiveness estimates?	The company Gompertz worsens the ERG corrected company base case ICER from £49,190 per QALY to £51,804 per QALY. The ERG ITT generalized gamma worsens the ERG corrected company base case from £49,190 per QALY to £52,548 per QALY.
What additional evidence or analyses might help to resolve this key issue?	None.

Issue 11: Censoring and the possibility of informative censoring

Report section	4.3.3.5
Description of issue and why the ERG has identified it as important	There is much higher censoring in GARNET than in the RWEQ data. If this pattern of censoring was observed in a two-arm trial it would be a major concern. Quite a lot of patients in GARNET were censored early in the trial.
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	If censoring in GARNET for reasons other than data cut - off did not occur at random but was in part associated with other factors such as patient baseline characteristics, patient response or patient disease type, the analysis would be biased in favour of dostarlimab.
What additional evidence or analyses might help to resolve this key issue?	GARNET patient baseline characteristics and KM data, with censoring events divided into those due to data cut-off and those for other reasons, split by best response.

1.6 *Other key issues: summary of the ERG's view*

Issue 12: Reliability of comparing GARNET with the RWEQ

Report section	4.3.3.6, 5.2 & 6.2
Description of issue and why the ERG has identified it as important	The ERG has performed exploratory cost effectiveness analyses by fitting curves to some of the RWEQ individual treatment KM data. This suggests that dostarlimab has a somewhat worse ICER when compared to the combination therapies. It also suggests that dostarlimab has a somewhat better ICER when compared to pegylated liposomal doxorubicin (PLD) monotherapy. But the company cost effectiveness estimate for dostarlimab against doxorubicin that used the ZoptEC trial has an ICER that is worse than the company base case ICER. This raises questions about the reliability of the comparison with the RWEQ data and whether it biases the analysis in favour of dostarlimab.
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	If GARNET has tended to recruit fitter patients or patients whose disease has a better prognosis than the RWEQ patients or there is a trial or placebo effect within GARNET the analyses will be biased in favour of dostarlimab.
What additional evidence or analyses might help to resolve this key issue?	GARNET and RWEQ KM data split by endometrioid status and ECOG performance status. RCT data.

1.7 *Summary of ERG's preferred assumptions and resulting ICER*

The ERG corrected company base case is as per Table 3, with an ICER of £49,190 per QALY. The corresponding central ICER of the probabilistic modelling is £48,764 per QALY.

Table 3: Summary of the ERG corrected company base case

	Current treatment	Dostarlimab	Net
Life years QALYs Costs	[redacted]	[redacted]	[redacted]
ICER			£49,190

The ERG preferred assumptions are outlined in Table 4.

Table 4: ERG preferred assumptions and model inputs

Preferred assumption	Section	ICER
Company base-case	5.1	£37,311
ERG corrected company base-case	4.3.1	£49,341
ERG01: Dostarlimab OS Weibull	4.2.6.5 4.3.3.2	£65,454
ERG02: Dostarlimab ERG ITT TTD GGAM	4.3.3.8	£52,709
ERG03: [redacted] dostarlimab continue	4.3.2.1 4.3.3.3	£49,341
ERG04: Waning from treatment cessation	4.3.2.1 4.3.3.3	£55,523
ERG05: Quality of life – no time to death coefficient	4.3.4.1	£49,513
ERG06: Ongoing resource use	4.3.4.6	£48,885
Cumulative effect: ERG02-ERG06	..	£64,006
Cumulative effect: ERG01-ERG06	..	£79,714

ERG: evidence review group; GGAM: generalised gamma; ICER: incremental cost-effectiveness ratio; ITT: intention to treat; OS: overall survival; TTD: time to treatment discontinuation

The ERG presents a range of scenario analysis.

- SA01: Assuming dostarlimab treatment cessation from [redacted] and from [redacted], retaining the assumption that all cease treatment at [redacted].
- SA02: Assuming proportions remaining on dostarlimab at [redacted] of [redacted] and [redacted].
- SA03: Assuming treatment waning starts [redacted] and [redacted] after the treatment cessation at [redacted].
- SA04 Applying the company Gompertz and company log-logistic dostarlimab TTD curves.
- SA05: Applying the dostarlimab TTD KM curve for the first 8 months of the model.
- SA06: Applying the quality of life values of the German study: PFS 0.701 and PPS 0.676.

- SA07: Applying a correction factor to the RWEQ treatment costs to align the modelled treatment duration with the mean stated by the company.
- SA08: Reducing the frequency of visits to the specialist nurse when in PFS off treatment to 12 weekly.
- SA09: Time horizons of 10, 20 and 30 years.

Given the importance of the choice of dostarlimab OS curve, the ERG scenario analyses are presented for the ERG preferred Weibull OS curve and for the company preferred generalised gamma OS curve.

Table 5: ERG scenario analyses

	ICER	
	Weibull	**Gen.Gamm.**
Base case	£79,714	£64,006
SA01a: Cessation at [redacted]	£81,853	£63,583
SA01b: Cessation at [redacted]	£83,990	£63,140
SA02a: [redacted] dostarlimab [redacted] continuing treatment	£73,411	£59,041
SA02b: [redacted] dostarlimab [redacted] continuing treatment	£83,336	£66,859
SA03a: Waning starts [redacted] after [redacted] cessation	£77,378	£60,153
SA03b: Waning starts [redacted] after [redacted] cessation	£75,813	£57,082
SA04a: Dostarlimab Gompertz TTD curve	£80,921	£64,733
SA04b: Dostarlimab log-logistic TTD curve	£75,198	£60,225
SA05: Dostarlimab KM TTD for 8 months	£75,457	£60,429
SA06: German QoL values	£79,263	£63,465
SA07: RWEQ treatment cycles adjustment	£80,083	£64,296
SA08: Reduced specialist nurse frequency	£79,290	£64,170
SA09a: 10 year time horizon	£90,563	£74,322
SA09b: 20 year time horizon	£81,822	£65,962
SA09c: 30 year time horizon	£79,911	£64,186

KM: Kaplan Meier; ICER: incremental cost-effectiveness ratio; TTD: time to treatment discontinuation

The ERG also analyses the RWEQ individual treatment data, which results in the cost effectiveness estimates of Table 6. There is a modelling issue as to whether dostarlimab treatment waning should be based upon the pooled RWEQ curves or upon the individual comparator curves. The ERG thinks that it should be based upon the individual comparator curves.

Table 6: ERG scenario analyses: Individual treatment comparisons

Waning	RWEQ curves used			Comparator curves used		
Comparator	Δ QALY	Δ Cost	ICER	Δ QALY	Δ Cost	ICER
Carb+Pac	[redacted]	[redacted]	£104k	[redacted]	[redacted]	£108k
Carb+PLD	[redacted]	[redacted]	£88,929	[redacted]	[redacted]	£102k
PLD mono	[redacted]	[redacted]	£53,080	[redacted]	[redacted]	£58,120
Carb+Pac: Carboplatin + paclitaxel, Carb+PLD: Carbplatin + PLD, PLD mono: PLD monotherapy						

Evidence Review Group Report

2 INTRODUCTION AND BACKGROUND

2.1 *Introduction*

This Evidence Review Group (ERG) report provides a detailed critique of the company submission (CS) presented to the National Institute for Health and Care Excellence (NICE) for the single technology appraisal (STA) on dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency. Related NICE STAs include the currently suspended pembrolizumab for previously treated endometrial cancer NICE technology appraisal [ID1205][1] and the ongoing lenvatinib with pembrolizumab for previously treated advanced endometrial cancer NICE technology appraisal [ID3811].[2]

Dostarlimab has been approved by the European Medicines Agency (EMA) in April 2021.

The ERG noted that the positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the EMA was for a conditional marketing authorisation, which is granted for a medicine that *"fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact that additional data are still required. The marketing authorisation holder is expected to provide comprehensive clinical data at a later stage*."[3]

The primary evidence that supported the conditional marketing authorisation and that forms the key part of clinical effectiveness evidence for dostarlimab in the CS for this STA is data from a single arm phase I trial, GARNET (Clinical Study Report dated July 2019 provided with the CS, and Oaknin et al. 2020[4]). Comparative effectiveness and cost-effectiveness between dostarlimab and current practice in the National Health Services (NHS) therefore need to be derived from indirect comparisons between data from GARNET trial and those sourced from elsewhere. Consequently, ERG's critique focuses on the limited volume of clinical evidence, the validity of indirect comparisons based on the evidence and associated

uncertainties related to the findings, and the derivation of cost-effectiveness estimates based on these.

2.2 *Background*

2.2.1 Endometrial cancer

The company provided detailed overview of endometrial cancer in CS Section B.1.3.1. Endometrial cancer forms the vast majority (94%) of uterine cancer, which is the 4th most common cancer and accounts for 5% of all new cancer cases in female in the UK.[5] The incidence of endometrial cancer peaks among 75-79 age group, with a total of 9,494 incident cases diagnosed in 2017 and an estimated prevalence of 70,200 women who had been diagnosed between 1991 and 2010 being still alive at the end of 2010.[5] Around 80% of uterine cancer are diagnosed at an early stage (I/II), with older age associated with late stage diagnosis.[5]

2.2.2 Marketing authorisation for dostarlimab

Dostarlimab is approved by the EMA "*as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen*".[6]

The targeting of patients with dMMR/MSI-H reflects the proposed mechanism of action for dostarlimab, which is an inhibitor of programmed cell death protein (PD-1) that is implicated in preventing immune cells to kill cancer cells.

2.2.3 Classification

EC has traditionally been classified into two types (Type I and Type II) proposed by Bokhman based on endocrine and metabolic features.[7] Classifications based on histology and molecular features of the tumours have subsequently been incorporated into the classification as described below. While it is acknowledged that the dualistic classification does not fully reflect the heterogeneity of EC which has become apparent with more recent knowledge particularly in genetic epidemiology,[8] the classification is a commonly used prognostic factor, the information of which is relatively easy to obtain.

Type I EC is moderately or well differentiated tumours associated with oestrogen excess, obesity, hormone receptor positivity and endometrial hyperplasia. Type I EC typically includes grade 1 and grade 2 endometrioid EC and constitutes around 60-70% of cases, who tend to have better prognosis.[9]

Type II EC is poorly differentiated tumours with low or absence of hormone receptor expression and is associated endometrial atrophy. Type II EC typically includes serous and clear-cell carcinoma and constitutes around 30-40% of cases, who tend to have worse prognosis.

2.2.4 Staging

Currently the most widely used staging for endometrial cancer is the classification proposed by the International Federation of Gynecology and Obstetrics (FIGO) in 2009[10] as shown in Table 7 below.

Table 7: FIGO staging for endometrial cancer

Stage	Description
I	**Tumour confined to the corpus uteri (i.e. the body of the uterus, or the womb)**
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium (middle layer of the uterine wall consisted mainly of muscle cells)
II	**Tumour invades cervical stroma (dense, fibromuscular tissue through which vascular, lymphatic, and nerve supplies to the cervix pass), but does not extend beyond the uterus**
III	**Local and/or regional spread of the tumour**
IIIA	Tumour invades the serosa of the corpus uteri (outer layer of uterus) and/or adnexae (the region adjoining the uterus that contains the ovary and fallopian tube)
IIIB	Vaginal and/or parametrial involvement (connective tissue that surrounds the uterus and connect the uterus to other tissues in the pelvis)
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IV	**Tumour invades bladder and/or bowel mucosa, and/or distant metastases**
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

Adapted from Pecorelli 2009.[10]

2.2.5 Prognostic factors

The company conducted a targeted literature review in which published literature reviews of prognostic factors associated with survival in EC were identified by Google searches (CS Appendix M). Adjustment for all potential prognostic factors and effect modifiers is required to minimise bias for unanchored indirection comparison that relies on data from individual arms from different studies as in this STA. Details regarding this are discussed in Section 3.4 of this report.

2.3 *Critique of company's definition of decision problem*

ERG's critique of company's definition of decision problem is shown in Table 8.

The population addressed in the CS is narrower than what was specified in the final scope in that patients are required to "have progressed on or following prior treatment with a platinum-containing" rather than simply "previously treated" EC. This stricter requirement seems to be in line with the marketing authorisation for dostarlimab received from EMA. However, ERG notes that relevant inclusion criteria specified in the GARNET trial clinical study report (CSR) are even more restrictive in that patients were required to:

- Have progressed on or after platinum *doublet therapy*.
- Have received *no more than 2 lines of anticancer therapy for recurrent or advanced (≥Stage IIIB) disease.*

These may have implications related to generalisability of GARNET trial evidence as well as selection of comparators for undertaking indirect comparison to generate estimates for relative effectiveness.

For comparator, the company used a basket of treatments found to be most commonly used in current clinical management according to real world evidence (RWE) obtained from UK registry in its base case. Treatment regimens included in the base case are broadly in line with comparators listed in the final scope, with the following exceptions:

- Pegylated liposomal doxorubicin (PLD) monotherapy was included instead of doxorubicin monotherapy.

- While hormone therapy was included in company's base case, no empirical data for its effectiveness was used as hormone therapy was not adequately captured in the registry and the literature review did not identify any studies that provided relevant evidence. Instead, an assumption that its effectiveness would be as good as the basket of chemotherapies was made.

- Carboplatin plus PLD was included in the basket of treatments in company's base case but was not listed in the final scope.

- Best supportive care was excluded from the company's decision problem.

Overall, the ERG considered the company's approach to using a basket of most commonly used treatments based on UK registry reasonable given the large number of diverse regimens used in clinical practice. However, this approach raises challenges in finding a patient population and retrieving data that are directly comparable with the well-defined GARNET trial population and data. Pertinent issues related to these are highlighted in Section 3 of this report. The ERG agrees that best supportive care is not particularly relevant in the targeted place in the treatment pathway.

While no patient subgroups were specified in the final scope of this STA and in the company submission (CS), the target population includes patients with advanced disease or patients with recurrent disease. As the company acknowledge (CS Section B1.3.2), these two groups of patients may different treatment history, and potentially different response to treatment and prognosis. Potential analyses stratified by these subgroups may reduce heterogeneity within the patient population included in this appraisal. Nevertheless, no such analyses were conducted and presented in the CS.

Table 8: Summary of decision problem addressed in the company submission and ERG's critique

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency.	Patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or following prior treatment with a platinum-containing regimen.	The patient population is aligned with the NICE final scope, though it is important to note that patients eligible for dostarlimab must *have progressed on or following prior treatment with a platinum-containing regimen*. This is in line with the marketing authorisation for dostarlimab in this indication and the patient population included in the pivotal GARNET trial (see CS Section B.2.3.1).	As the company highlighted, the additional eligibility criterion regarding prior treatment with a platinum-containing regimen conforms to the marketing authorisation granted by the EMA and reflects the inclusion criteria of the GARNET trial. The company suggests that platinum-containing regimen is a standard of care in the UK for first-line treatment for recurrent or advanced EC (CS Section B.1.3.4.2). ERG agrees with this.
Intervention	Dostarlimab	Dostarlimab	NA – aligned with the NICE final scope.	No concern.
Comparator(s)	**Chemotherapy**, including: • Carboplatin and paclitaxel	**Base case cost-effectiveness analysis:** A basket of treatments representing current clinical management, comprising:	**Current clinical management** • In the absence of a definitive standard of care or clear treatment guidelines for this indication, the base case cost-effectiveness analysis	ERG recognises that there is no definitive guideline for the choice of treatment in this setting, and various combination and monotherapy including

	• Paclitaxel monotherapy • Doxorubicin monotherapy • Carboplatin monotherapy **Hormone therapy** (such as medroxyprogesterone acetate and megestrol) **Best supportive care**	• Carboplatin plus paclitaxel • Paclitaxel monotherapy • Carboplatin plus pegylated liposomal doxorubicin (PLD) • PLD monotherapy • Carboplatin monotherapy • Hormone therapy (50:50 ratio of medroxyprogesterone and letrozole) **Scenario analyses:** Individual comparisons versus: • Carboplatin plus paclitaxel • Paclitaxel monotherapy • Doxorubicin monotherapy • Carboplatin monotherapy • Hormone therapy (50:50 ratio of medroxyprogesterone and letrozole)	compares dostarlimab to current clinical management in the UK as a basket of comparator therapies. This consists of aggregate data for patients receiving a range of the most commonly prescribed chemotherapy regimens in patients with recurrent or advanced EC who have progressed on or after a platinum-containing regimen in clinical practice, based on a GSK-initiated real-world evidence (RWE) study using data from the National Cancer Registry Analysis System (NCRAS) in England (hereafter referred to as the UK RWE study). • The treatments included in this aggregate data include the individual chemotherapy regimens listed in the final scope, as well as carboplatin plus PLD. As the UK RWE study could not capture hormone therapy, the costs of hormone therapy (a weighted average of medroxyprogesterone acetate and letrozole based on UK clinical expert feedback) have instead been	platinum-based chemotherapy (e.g. carboplatin and cisplatin), anthracyclines (e.g. doxorubicin) and taxanes (e.g. paclitaxel, docetaxel) have been used in clinical practice depending on characteristics of the tumour, individual patient's treatment history, fitness and other factors. Ideally, comparison of dostarlimab with individual comparators would allow more precise evaluation of relative effectiveness and cost-effectiveness which take into account potential association between patient characteristics and treatment choice. Nevertheless, the large number of possible regimens and the paucity of effectiveness data related to individual regimens mean comparison with individual comparator may only be feasible for most commonly used regimens such as carboplatin + paclitaxel and doxorubicin monotherapy. Given the

			incorporated within the basket. • An SLR was conducted to identify relevant clinical evidence for the individual therapies listed in the NICE final scope however these data were extremely limited; most studies in the relevant patient population were observational studies, where patient characteristics and Kaplan-Meier (KM) survival data were poorly reported. Where possible, scenario analyses have been conducted versus the comparators for which data were identified in the literature in the post-platinum chemotherapy setting. • No data were identified for either carboplatin monotherapy or hormone therapy. Despite efforts made to identify alternative sources of data for these comparators, feedback from UK clinical experts strongly indicated that any data for patients not in the post-platinum chemotherapy setting would not be suitable to use as a proxy for these comparators. The UK clinical	above consideration, ERG agrees that using a basket of treatments found in current practice may be a reasonable comparator. ERG considers that hormone therapy is a relevant comparator in second-line, recurrent or advanced EC setting. ERG agrees that patients who would be considered for best supportive care alone are likely to be those who are not well enough to be considered for dostarlimab treatment, and therefore best supportive care is not a relevant comparator in the targeted place in the treatment pathway.

			experts also indicated that survival with hormone therapy or carboplatin monotherapy would not be expected to exceed that observed in the UK RWE study. As such, individual comparisons have been explored between dostarlimab and carboplatin monotherapy and hormone therapy in scenario analyses, using efficacy data for doxorubicin monotherapy and current clinical management as a proxy, respectively (See Section B.3.8.3). **Removal of BSC** • BSC was not fully defined in the NICE final scope, and there is a lack of standardised definition in the literature. It is likely to consist of pain and symptom management or relief with treatment such as analgesics and corticosteroids. • BSC is not considered a relevant comparator to dostarlimab in this submission and a comparison versus BSC has not been included, for the following reasons:	

			o Feedback from UK clinical experts is that, for most patients, BSC would be used as an add-on therapy to chemotherapy and thus is expected to be used as an add-on therapy to dostarlimab.16 Accordingly, UK clinical experts agreed that BSC would not represent a relevant comparator to dostarlimab.16 o Whilst a small proportion of patients with recurrent or advanced EC who have progressed on or after a platinum-containing regimen may receive palliative therapy as BSC, these patients reflect a different patient population (of more severely unwell patients) compared to the proposed target population for dostarlimab.	
Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rates • duration of response	• Progression-free survival • Overall survival • Response rates (overall response rates, disease control rate) • Duration of response	NA – aligned with the NICE final scope.	No concern.

	• adverse effects of treatment • health-related quality of life	• Adverse effects of treatment • Health-related quality of life		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment	• An economic analysis has been conducted with the cost-effectiveness of treatments expressed in terms of incremental cost per quality-adjusted life year. • A lifetime time horizon has been adopted to reflect all differences in costs and outcomes between the technologies being compared. • Costs are considered from an NHS and Personal Social Services perspective. • A confidential commercial discount to the list price of dostarlimab has been adopted within the base case analysis. • Any commercial arrangements for the comparators are not	• Regarding the costs associated with diagnostic testing, NICE diagnostics guidance DG42 recommends that all patients with EC should be tested using immunohistochemistry (IHC) to identify tumours with dMMR/MSI-H.18 DG42 recommends that IHC testing for dMMR is the preferred approach, and clinical expert opinion sought by GSK agreed with this.16 Additionally, discussions with NHSE at a surgery confirmed that testing would not be an issue for access to dostarlimab. • Furthermore, given the availability of nivolumab through the Cancer Drugs Fund (CDF) for patients with dMMR/MSI-H, dMMR testing is already in use in clinical practice to identify eligible patients, and therefore resources for dMMR testing are already being embedded within usual practice. • As such, dMMR testing will soon become standard of care for all patients with EC and no additional diagnostic tests will be	The ERG agrees that test costs should not be included.

	technologies will be taken into account. The economic modelling should include the costs associated with diagnostic testing for microsatellite instability status in people with endometrial cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.	known and have therefore not been taken into account. • The inclusion of diagnostic testing for dMMR/MSI-H status has been explored within a scenario analysis, which considers dMMR/MSI-H testing for recurrent patients only (see Section B.3.8.3).	required to facilitate the prescribing of dostarlimab beyond those already conducted for patients with EC in UK NHS clinical practice. These costs have therefore not been included within the base case economic analysis, but a scenario analysis has been conducted to explore the impact of the inclusion of diagnostic testing costs for dMMR status for recurrent patients only.	
Subgroups	None specified	Not discussed in the CS.	No comments provided.	The target population includes two subgroups of patients (i.e. patients with advanced or recurrent disease) with different treatment history and prognosis, and could potentially be evaluated separately.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific	Not discussed in the CS.	No comments provided.	No concern.

	treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.			

3 CLINICAL EFFECTIVENESS

3.1 *Critique of the methods of review(s)*

The company conducted an original and updated clinical systematic review to identify evidence for the efficacy and safety of dostarlimab and the chemotherapy comparators listed in the NICE final scope for the treatment of recurrent or advanced EC that has progressed on or after platinum-based chemotherapy. A range of study types (both interventional and observational) are included (CS Appendix D.4.1).

A summary of the ERG's quality assessment of the company's systematic review of clinical evidence is presented in ERG report Appendix (Table 57). While the overall risk of bias was judged to be low, the ERG has some concern. The company did not use the NICE-preferred tool for assessing methodological quality, heterogeneity in study results was not addressed in their analysis, and no information on predefined analyses in a referenced protocol or in the submission was provided. Results from the clinical systematic review were analysed with narrative description. Given the nature and differences in the study designs and outcomes across included studies, a quantitative synthesis may not be appropriate. The ERG considers the narrative analyses method appropriate for the SLR.

The company did not initially consider hormone therapy (which was within the NICE final scope) as one of the comparators, and thus was not included in the original or update clinical SLR. However, the company provided a targeted literature review (TLR) for hormone therapy (CS Appendix L). A summary of the ERG's quality assessment of the company's the hormone therapy TLR is presented in the ERG report Appendix. No studies from the hormone therapy TLR were found relevant by the company for this submission; thus, none was included in the cost-effectiveness analysis. The company made an assumption that hormone therapy has the same effectiveness as other therapies in the basket of

treatments was made; thus, conducted a scenario analysis with hormone therapy, using the UK RWE study as a proxy to validate the base-case.

The ERG examined the studies included and excluded in the company's clinical systematic review as well as the hormone therapy TLR. In addition, the ERG conducted searches for recent relevant systematic reviews and examined their bibliographies for studies of comparator treatments listed in the NICE final scope. No additional relevant studies were identified by the ERG.

Quality Assessment

The company states that they assessed study quality using the Appendix C of PMG6 methodology checklist for randomised controlled trials in the old NICE guidelines manual,[11] Critical Appraisal Skills Programme (CASP) check list for Non-RCTs,[12] and ROBINS I assessment tool for the UK RWE study (non-RCT study)[13] (CS section B.2.3.1.4 and Appendix D.7). The latest NICE guidance[14] recommends the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) checklist for RCTs, and the Institute of Health Economics (IHE) Quality Appraisal Checklist for case series (non-RCTs). Therefore, the ERG conducted an independent assessment of the eight studies included in the indirect treatment comparisons (ITCs) (GARNET, UK RWE study, ZoptEC trial, McMeekin *et al*. (2015), Rubinstein *et al*. (2019), Mazgani *et al*. (2008), Julius *et al*. (2013), and Makker *et al*. (2013))[15-21]) using both tools. A comparison of the ERG and company quality assessments using the company's preferred tools are provided in ERG report appendix (Table 58, Table 59, Table 60 respectively). A single ERG reviewer conducted these assessments, with a second reviewer checking all items where the ERG and company disagreed.

ERG points of critique: The ERG has few concerns over the overall low risk of bias of company's clinical SLR. In addition to the observed differences between the ERG and the company's judgements, the choice of checklist for the quality appraisal appears to be important given the differences in ERG overall risk of judgments using the company preferred checklist compared to the NICE preferred checklist, particularly for GARNET, where the ERG reported a low risk of bias rating using NICE preferred checklist and moderate risk rating using the company preferred check list. GARNET is noted to be of higher quality compared to the UK RWE study (the key comparator study), using the NICE preferred checklist.

3.2 *Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)*

The key study in the CS is the GARNET (NCT02715284), a Phase 1, single-arm, open-label, multicentre, non-randomised study of dostarlimab (see ERG report Appendix for details on the study quality assessment).

GARNET (data cut 1 March 2020) has not previously been published and data are presented in the CS and the CSR provided to the ERG.

3.2.1 GARNET trial

3.2.1.1 GARNET method

GARNET is an ongoing multi-cohort study conducted in 9 countries (including 9 centres in UK) to evaluate the antitumor activity of dostarlimab in participants with recurrent and advanced endometrial cancer with only the relevant Cohort A1 included in the submission. This cohort included patients with recurrent or advanced dMMR/MSI-H EC that has progressed after treatment with a platinum-containing chemotherapy regimen and have histologically or cytologically

proven recurrent or advanced EC with measurable lesion(s) per RECIST v1.1.[22] Patients had to have received no more than 2 lines of anticancer therapy for recurrent or advanced (≥Stage IIIB) disease. All EC histologies were allowed, except endometrial sarcoma. Participants were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and adequate organ function. Key exclusion criteria were prior therapy with an anti-PD-1, anti-PD-L1, or anti-programmed cell death-ligand 2 agent, uncontrolled central nervous system metastases and/or carcinomatous meningitis, and additional malignancy that progressed or required active treatment within the last 2 years. CS Appendix N, Table 96 has detailed patient eligibility criteria. The key patient flow of the study is provided in CS Appendix D.6 Table 64.

Eligible patients received dostarlimab 500 mg via IV infusion every 3 weeks (Day 1 of each 21-day cycle) for the first 4 cycles, followed by dostarlimab 1000 mg via IV infusion every 6 weeks (Day 1 of each 42-day cycle) for all subsequent cycles. The median follow-up in the submission was [redacted] months (see CS section B.2.4 for follow-up for specific outcomes). The ERG considered this a relatively short follow-up duration. 129 patients received any amount of dostarlimab (intention-to-treat (ITT) population/safety analysis set). This population was used in the base case cost-effectiveness evaluation. The company described a number of pre-specified analysis populations, including: the efficacy population analysis set (n = [redacted]) and immune-related efficacy population set (n = [redacted]) (CS Table 8).

Baseline characteristics of the participants in GARNET were reported by the company for the ITT population/safety and efficacy population analysis sets, discussed in more detail in CS section B.2.3.1.2 (CS Table 7). The ERG verified these data using the tables and figures provided by the company in the submission as these were not reported in the company CSR. [redacted] patients received more than 2 prior lines of anticancer therapy for recurrent or advanced disease, which appear to contradict with the specified inclusion criteria of no more than 2 prior lines of anticancer therapy (CS Appendix

N). The company explained in factual accuracy check that the 2 prior lines of anticancer therapy for trial inclusion refer specially to platinum-based therapy. However the ERG could not verify this based on the published trial protocol. The ERG considered the inclusion of these [redacted] patients important as it is unclear if any adjustments were made in the indirect comparisons (CS Appendix D.5).

The clinical advisors consulted for the ERG considered the GARNET participants to be generally representative of UK patients (CS section B.2.3.1.2, CS Table 7).

3.2.1.2 Efficacy outcomes

The company describes the primary and secondary efficacy outcomes in CS Table 6. Key safety measures and health-related quality of life (HRQoL) outcome measures are also described in CS Table 6.
For the key efficacy outcomes, the efficacy evaluable set (n=[redacted]) was used, excluding progression free survival (PFS) and overall survival (OS), where the ITT population/safety set was used in the economic evaluation (n =129). For immune-related efficacy outcomes, a different population was used (n=[redacted]). HRQoL and safety outcomes were also derived from ITT population/safety set. As GARNET is a single arm study, the statistical assessment of outcomes was descriptive. Kaplan-Meier methods were used to estimate PFS and OS.

Table 9: Key efficacy outcomes from GARNET, summarises the key clinical effectiveness outcomes of GARNET. Fuller details are presented in the CS section B.2.4.1, B.2.4.2, B.2.4.3, B.2.4.5 – B.2.4.8.

Table 9: Key efficacy outcomes from GARNET

Efficacy outcomes	**Efficacy evaluable set, (n=); ITT population (n=129)***
ORR (95% CI)[a]	
Complete response	
Partial response	
DOR, median (95% CI)[b] months Median follow-up months	
DCR (95% CI)[a]	
irORR[c,d]	
irDOR[c,e] median (95% CI) months	
irDCR[c,d]	
*PFS[b], median (95% CI) months Median follow-up months	
irPFS[c,d], median (95% CI) months	
*OS[b], median (95%) CI months Median follow-up months	

Footnotes: [a]Two-sided 95% exact Clopper–Pearson confidence interval (CI); [b]Two-sided 95% CI from Kaplan–Meier; [c] Immune-related efficacy population; [d]Exact 2-sided 95% CI for the binomial proportion; [e] 95% CIs from Brookmeyer and Crowley (1982) method; *ITT population;**PFS estimate from non-rounded up individual patient PFS estimates; +indicates response is still ongoing
Abbreviations: ORR: Overall response rate; DOR: Duration of Response; DCR: Disease control rate; irORR: immune-related ORR; irDOR: immune-related DOR; irDCR: immune-related DCR; irPFS: immune-related PFS; PFS: Progression Free survival; OS: Overall Survival.

The ERG verified the above data using the tables and figures provided by the company in the submission and the CSR. The ERG could only verify PFS, irPFS and OS information for the ITT population using the tables and figures provided by

the company in the submission as these were not reported in the company CSR. The company reported immune end points to provide more specific information for the tumour response to dostarlimab as an immunotherapy. The ERG agrees with this rationale. The ORR majorly consisted of partial response. The median DOR was not reached. The median PFS was associated with very wide confidence intervals (CIs) and was very sensitive to very small changes in individual patient PFS estimates, leading to different PFS estimates for rounded up and unrounded up individual patient PFS estimates. Median PFS estimate of [redacted] months (from non-rounded up individual patient PFS estimates) informed the economic evaluation. Most of the progression occurred in the first 6 months. The median OS was not evaluable. Figure 1 and Figure 2 below show progression free survival (PFS) and overall survival (OS) from GARNET. The blue lines are the survival outcomes for the ITT/safety population. PFS and OS information from the ITT population/safety set (n =129) was used in the economic evaluation. The ERG notes that the flat tail in GARNET OS curve is predictive of long term effectiveness; however, it may be due to insufficient follow-up duration/immature data, and small sample size.

Figure 1: PFS from GARNET (efficacy population and ITT population) (BICR)

Figure 2: OS from GARNET (efficacy population and ITT population)

The CS presents pre-specified subgroup analyses for ORR in the efficacy population in CS Figure 20. There appears to be overlapping 95% CIs within the subgroups as well as with the overall population ORR. However, this was not observed for the subgroup analysis by ECOG performance status. The ERG agrees with the company that ORR was ≥20% (null hypothesis; expected ORR for conventional therapy) for all of the subgroup estimates, suggesting a treatment benefit of dostarlimab for all subgroups. However, the ERG notes that numbers for many of these subgroups are small with wide confidence intervals suggesting uncertainty. The ERG could only verify these data using the figure provided by the company as there was no information in the CSR.

ERG points of critique: Patients with more than 2 lines of prior anti-cancer treatment were included in the GARNET study, which was not consistent with the pre-specified eligibility criteria. Clinical effectiveness outcomes were reported

over a relatively short time frame and have the potential for positive response to treatment with dostarlimab in most participants. Some outcomes do not have enough data to be fully reported (such as DOR and OS). The median PFS is unstable and varies with the decimal place of individual PFS estimates. With no comparator group it is unclear what magnitude of benefit dostarlimab offers over established clinical management. This is discussed in more detail in Section 3.4 of the ERG report (Critique of the indirect comparison).

3.2.1.3 HRQoL

The EORTC-QLQ-C30 and the EQ-5D-5L were assessed following a protocol amendment, and therefore not all participants were assessed for the effects of dostarlimab on HRQoL. The HRQoL data was from participants in the ITT/safety population set. No HRQoL outcomes are reported in the CSR provided by the company. The ERG could only verify these data using the tables and figures provided in CS section B.2.4.8. For EORTC-QLQ-C30, [redacted] participants had evaluable data and the mean scores generally showed improvement in HRQoL from baseline to week 24, except for deterioration in some domains in the initial month (CS section B.2.4.8). The ERG notes that not all domains and items of the EORTC-QLQ-C30 were reported. Over the period of follow-up, the minimally important difference appears to be achieved by patient-reported pain, fatigue symptoms, physical functioning, and symptomatic adverse events (AEs). For the EQ-5D-5L index score, [redacted] participants had evaluable data. The change from baseline was submitted by the company in response to clarification question A12b, where the initial 18 weeks showed improvements, followed by fluctuation to week 54, and thereafter an improvement to week 78 with a decline to week 96. These EQ-5D-5L scores were used in the economic evaluation, see CS section B.3.4.1 for further description. For the EQ-VAS, [redacted] participants had evaluable data. The change from baseline is seen in CS Figure 16, where mean scores showed fluctuation throughout the study. The most notable improvement in the scores were seen after end of treatment. The ERG notes that a small number of participants were evaluated from week 18 onwards.

ERG points of critique: The effects of dostarlimab on HRQoL is unclear. Not all participants were assessed for HRQoL, the CS does not report the mean change from baseline for all domains of the EORTC-QLQ-C30 and no discussion of the minimally important differences of these outcomes were reported.

3.2.1.4 Safety

The safety data reported were from the dostarlimab ITT/safety population set, n=129 as a secondary outcome in the CSR and CS section B.2.8. Most participants receiving dostarlimab had at least one treatment-emergent adverse event (TEAE) ([redacted]) and [redacted] experienced at least one Grade 3 or higher TEAE. Serious adverse events occurred in [redacted] of patients. The most frequently reported Grade ≥3 TEAEs were anaemia and abdominal pain, see CS Table 34. Grade ≥3 TEAEs with an incidence of ≥5% were included in the economic model, see CS section B.3.3.8. Death occurred in participants ([redacted]) while in the study, with disease progression as the most common reason ([redacted]129, [redacted]). Adverse event was the cause of death in [redacted] patients.

ERG points of critique: The ERG clinical advisors considered the toxicity of dostarlimab to be at an acceptable rate for an immunotherapy (I-O therapy).

3.3 *Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

Evidence for the comparator is taken from a real-word evidence (UK RWE) study which was funded by GSK (the company). Data for this study are provided in the CS and a report provided to the ERG in response to clarification question C2. In addition, six studies (Rubinstein *et al*. (2019); Mazgani *et al*. (2008); McMeekin *et al*. (2015); Julius *et al*.

(2013); Makker *et al*. (2013); and ZoptEC study)[15-21] were included in the indirect comparison and used by the company in scenarios for the economic model (see CS section B.3.8.3).

3.3.1 UK RWE study

The UK RWE study was used as the main comparative evidence (for current clinical management) in the indirect treatment comparison and economic model. It has not previously been published and data are presented in the CS and a report provided to the ERG in response to clarification question C2.

The UK RWE study was a UK national retrospective observational study (see ERG report Appendix for details on the study quality assessment), conducted by GSK to fill evidence gaps relating to the current clinical management for patients diagnosed with recurrent or advanced EC in the UK due to the lack of data identified for comparator therapies in the company's clinical SLR (CS section B.2.3.2 and B.2.4.5). UK RWE study used routine, linked patient-level UK health data available through the National Cancer Registration and Analysis Service (NCRAS), which combines linked data from several health and population databases. UK RWE study collected data for patients diagnosed between 1st January 2013 and 31st December 2018, with data extraction up until 30th September 2020.

To identify patients with EC, the UK RWE study used an initial inclusion criteria and exclusion criteria (CS Table 10). In addition, more inclusion and exclusion criteria were applied to identify patients with recurrent or advanced EC (CS Table 11). Further inclusion and exclusion criteria were applied to align the patient population more closely to GARNET (CS Table 12 and Appendix O.1). The key inclusion criteria for the UK RWE study to align the patient population more closely to GARNET included: a diagnosis of recurrent or advanced EC, and patients who received exactly one prior platinum doublet therapy for recurrent or advanced disease. The study identified a large population of patients (n=[redacted]), further known as UK RWE GARNET-like cohort or abbreviated as RWEQ (Real World EQuivalent) cohort for brevity in the ERG

report. The ERG notes that there are uncertainties around the impact of the possible selection bias associated with the complex process of deriving the UK RWEQ cohort from the patients with EC diagnosis in the registry. Figure 3 shows a flow of patients included in the RWEQ.

Figure 3: Patients included in the UK Real World EQuivalent (RWEQ) cohort (reproduced from CS Figure 8)

Abbreviations: 2L: second-line; EC: endometrial cancer; RWE: real-world evidence.

3.3.1.1 UK RWE study methods

The inclusion criteria of the GARNET trial and UK RWE study have been considered by the ERG. The key eligibility criteria for GARNET were presented in CS Table 6 (and Appendix N.1, Table 96) and the UK RWE in CS Table 10 - 12 and Appendix O.1.

The ERG notes that these criteria appear to be similar on many key factors but that there are differences; those with potential relevance are:

- In GARNET, participants were required to have received no more than two lines of systemic anticancer therapy. In the UK RWE study, the requirement was for exactly one prior platinum doublet therapy. Based on the company's response to ERG clarification question A15, the ERG considers the definitions of lines of prior therapy dissimilar

between GARNET and the UK RWE study. Adjuvant and neoadjuvant chemotherapy were excluded from the data shown in CS Table 7 for GARNET, but this could not be verified in the UK RWE study. Also, it was not required to have platinum-based doublet therapy as the last line of therapy prior to dostarlimab in GARNET. In the UK RWE study, it was required to have received only one line of platinum-based doublet chemotherapy, progressed, and received further second line treatment. Given the differences in the demographic and clinical baseline characteristics (see Table 10 below) between the two studies, it is unclear how the differences in the prior lines of therapy may impact the benefit of dostarlimab over established clinical management.

- In GARNET, participants were required to have histologically or cytologically proven recurrent solid tumour with measurable lesion(s) per RECIST v1.1. In the UK RWE study, the requirement for recurrence was probable recurrence, defined as patients who were FIGO Stage I/II and received surgery, systemic anti-cancer therapy or radiation therapy and then had a treatment gap greater than 90 days, followed by treatment with any treatment. The company notes that this definition was supported by their clinical advisors/UK clinical expert opinion; however, the ERG's clinical advisor noted that some sort of radiographic evidence is required to confirm recurrence.

  Based on company's response to ERG clarification question A16, the ERG has been able to consider the validity the definition of recurrence in the UK RWE study with the number of patients identified in the UK RWE study compared to the estimated incidence of patients with recurrent EC based on published epidemiological estimates for the UK which was submitted. The ERG notes that these estimates appear to be similar, but some uncertainty remains in the robustness of the definition of recurrence in the UK RWE study as a difference of about 2% in recurrence rate was observed when recurrence was defined as >180 days in the post-hoc sensitivity analyses conducted by the company in response to ERG clarification question A16. It is unclear how the difference in definition of recurrence between GARNET and UK RWE study might impact baseline prognosis.

- In GARNET, patients were required to have dMMR/MSI-H EC, this was not stated in the eligibility criteria for the UK RWE study. The CS states that "*MSI-H or dMMR EC represents a subgroup where PD-1/PD-L1 inhibition with I-O therapy (such as dostarlimab) is most effective*". Also, the company referred to a systematic literature review (SLR) conducted by GSK,[23] stating "there is no evidence MSI-H or dMMR biomarker status has any prognostic or predictive value for efficacy and survival outcomes (including recurrence, relapse-free survival, PFS and OS) among patients with advanced or recurrent EC receiving non-anti-PD-(L)1 therapy". The ERG notes that the full report for the SLR was not provided by the company. While ERG is not aware of evidence which contradicts this claim, ERG's clinical advisor pointed out that the inclusion of exclusively patients with dMMR/MSI-H in the GARNET may have resulted in the selection of a higher proportion of patients with better prognosis compared with RWEQ cohort, which was not selected based on MMR/MSI status. This is because dMMR/MSI-H is predominantly found within in Type I endometrioid tumours (28-40%), which tends to have better prognosis (as described earlier in Section 2.2.3) and is rarely found within other histological subtypes (serous, clear cell and other types, 0-2%) which tends to be more aggressive.[8] The was reflected in the much higher proportion of patients with endometrioid EC in the GARNET compared with RWEQ (see Table 10 below).
- In GARNET, participants were required to have adequate organ function; this was not stated in the eligibility criteria for the UK RWE study. This could also have led to the selection of fitter patients with better prognosis into the GARNET trial.

Demographic and clinical characteristics of the participants in the RWEQ cohort were reported by the company (CS section B.2.4). The ERG verified these data using the tables and figures provided by the company in the submission as there was no published study report for the RWEQ cohort. In the RWEQ, patients were required to have an ECOG PS of ≤1. However, patients with an ECOG PS of 'not recorded (NR)' (n=[redacted]) were not excluded by the company from the UK

RWEQ cohort for the purpose of a larger sample size of patients, longer follow-up, and prevention of potential unknown bias associated with non-recording. The company highlighted that information on the classification of patients as ECOG PS of 'not recorded' is not provided in the NCRAS dataset and the chances that patients with an ECOG PS of 'not recorded' had an ECOG PS >1 was negligible as patients with an ECOG PS >1 comprised a small percentage (N=[redacted]) of the overall UK RWE study patients with recurrent or advanced EC. The ERG has not been able to verify this estimate. The company provided a sensitivity analysis of patients with a known ECOG PS of 0 or 1 in the RWEQ cohort subsequently referred to as 'RWEQ ECOG PS ≤1' cohort (CS Appendix O.2 and reproduced in ERG report Table 6). The ERG agrees that the overall patient characteristics and efficacy outcomes of the RWEQ ECOG PS ≤1 cohort appear to be similar to the RWEQ cohort and excluding patients with an ECOG PS of 'not recorded' does not seem to have a major impact.

The ERG notes that the most common chemotherapy regimens received by patients also appear to be similar between REWQ ECOG PS ≤1 cohort and the RWEQ cohort (CS Table 14 and Appendix Table 128). The ERG observed that despite that carboplatin plus pegylated liposomal doxorubicin (PLD) was not listed in the NICE final scope as a relevant comparator, it was included by the company. The company noted data completeness as carboplatin plus PLD was received by a substantial proportion of the RWE population as the rationale for inclusion.

The ERG found several differences in the demographic and clinical baseline characteristics between the RWEQ cohort and GARNET ITT population (see Table 10 below) for the following characteristics: age (younger population in GARNET); FIGO stage (RWEQ population had more advanced disease); Grade of disease (highest portion was grade 3 in the RWEQ population, and grade 2 in the GARNET population); ECOG PS (GARNET had higher proportion in ECOG status 0 and 1, and half of the RWEQ population had their ECOG status unknown); histology (GARNET had a higher proportion

of endometroid disease); prior lines of therapy (RWEQ population had exactly one prior platinum doublet therapy while GARNET may have had 1 or more than prior lines of therapy, where one prior therapy must be specific to platinum doublet therapy); and prior surgery (GARNET had higher proportions). It is unclear how exactly these imbalances might affect baseline prognosis at the start of the second-line treatment and therefore subsequent outcomes in advanced/recurrence setting for the two groups, although many of the above differences may suggest more advanced and aggressive disease among the RWEQ cohort.

The ERG found differences in the company's presentation of patients' ECOG PS and FIGO stage. The company provided information on the ECOG PS and FIGO stage at study entry for GARNET whereas the ECOG PS and FIGO stage recorded at "registry diagnosis" was provided for the RWEQ study participants (see Table 10 below). The company explained in their response to ERG clarification question A20 that registry diagnosis is "the date a patient is entered in the NCRAS registry, and not necessarily the date of cancer diagnosis". As both ECOG PS and FIGO stage are well recognised prognostic factors and they may have changed (likely deteriorated) between registry entry and start of second-line therapy, ERG considered the discrepant timing of measuring these variables between GARNET and RWEQ to be a crucial issue that could invalidate any adjustments made in the indirect comparisons using these data (this issue is discussed further in Section 3.4.1).

Differences in the PFS time definition between RWEQ participants and the GARNET participants were also observed by the ERG. Time to next treatment (TTNT) was used as a proxy for PFS for the RWEQ due to lack of progression information within the NCRAS database and following advice from the company's clinical experts. The CS anticipates using TTNT as proxy for PFS may favour current treatment management. The ERG notes that there is uncertainty around the robustness of this proxy measure.

Table 10: Baseline characteristics and efficacy outcomes in the GARNET-like ECOG PS ≤1, UK RWE GARNET-like (RWEQ) cohort, and GARNET ITT population

Characteristic	GARNET-like UK RWE (RWEQ) ECOG PS ≤1 cohort (N=[redacted])	GARNET-like UK RWE (RWEQ) cohort (N=[redacted])	GARNET ITT population (N=129)
Mean age, years (STD)	[redacted]	[redacted]	[redacted]
Median age, years (range)	[redacted]	[redacted]	[redacted]
Age group, n (%)			
<65 years	[redacted]	[redacted]	[redacted]
65 to <75 years	[redacted]	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Most recent ECOG PS at registry diagnosis (RWEQ) or study entry (GARNET), n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Not recorded	[redacted]	[redacted]	[redacted]
Histology at diagnosis, n (%)			
Endometrioid	[redacted]	[redacted]	[redacted]
Non-endometroid	[redacted]	[redacted]	[redacted]
Serous carcinoma	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
FIGO stage at the time of registry diagnosis (RWEQ) or Most recent FIGO stage at study entry, (GARNET), n (%)			

I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Grade of disease at diagnosis, n (%)			
Grade 1	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Prior anticancer treatment, n (%)			
Any prior anti-cancer treatment	[redacted]	[redacted]	[redacted]
Prior surgery	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy post advanced/recurrent diagnosis, n (%)			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
≥4	[redacted]	[redacted]	[redacted]
Most common chemotherapy regimens			
	Carboplatin plus paclitaxel	Carboplatin plus paclitaxel	NA
	Carboplatin plus PLD	Paclitaxel monotherapy	NA
	Paclitaxel monotherapy	Carboplatin plus PLD	NA
	PLD monotherapy	PLD monotherapy	NA
	Carboplatin monotherapy	Carboplatin monotherapy	NA

	Cisplatin plus doxorubicin	Cisplatin plus doxorubicin	NA
	Carboplatin plus gemcitabine	Carboplatin plus gemcitabine	NA
	Doxorubicin monotherapy	Carboplatin plus doxorubicin	NA
	Cisplatin monotherapy	Doxorubicin	NA
	Carboplatin plus doxorubicin	Cisplatin	NA
Median PFS (months) (95% CI)	[redacted]	[redacted]	[redacted]
Median OS (months) (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynaecology and Obstetrics; ITT: intention-to-treat; RWE: real-world evidence; STD: standard deviation; NA: Not applicable

The ERG notes that hormone therapy is not included as part of the current clinical management of recurrent or advanced EC in the UK RWE study, and aware that it was incompletely captured in the NCRAS database. This is further verified through the company's response to clarification question A14, where the company re-iterated that patients receiving hormone therapy were not purposely excluded from the RWEQ cohort, rather hormone therapy was poorly reported in the NCRAS database, as it is dispensed in primary care or community pharmacies.

3.3.1.2 UK RWE study results

The primary efficacy outcome measures of the UK RWE study are PFS and OS. Safety measures were not recorded in the UK RWE study. As the UK RWE study is a single arm, retrospective observational study, the statistical assessment of outcomes was descriptive. Kaplan-Meier methods were used to estimate PFS and OS. Summaries of the PFS and OS outcomes from the final RWEQ cohort are presented in Table 10 above. The ERG verified these data using the tables and figures provided by the company in the submission. PFS and OS information from the RWEQ cohort was used in the cost effectiveness analysis. A naïve comparison of RWEQ cohort versus GARNET trial patients (CS section B.2.4.5.2 and B.2.4.6.2) showed RWEQ cohort had an increased risk of death, and a reduced risk of progression before month 9. The ERG notes that the results of the native comparison should be treated with caution due to the methodological differences in PFS definitions as well as the sensitivity of GARNET's PFS estimates and immaturity of the GARNET trial data.

ERG points of critique: Overall, the ERG notes there is considerable uncertainty as to the similarity between the RWEQ cohort and GARNET ITT population and its representation of the UK population. In addition, there are concerns about the appropriateness of the definition of recurrence and using TTNT as a proxy for PFS. In order to characterise the differences between GARNET and RWEQ cohort and to identify potentially more comparable patients between the cohorts, data stratified by advanced versus recurrent diseases, and by endometrioid versus other diseases for both cohorts may be valuable. The ERG requested these data as part of the clarification questions; however, no data was provided.

3.3.2 Published studies identified from the company's clinical SLR and included in the indirect comparisons

The UK RWE study was the main comparative efficacy evidence submitted by the company. However, indirect treatment comparisons (ITCs) between dostarlimab and comparators listed in the NICE final scope (including: carboplatin plus

paclitaxel, paclitaxel monotherapy and doxorubicin monotherapy) were carried by the company, based on the studies identified in the clinical SLR (including: Rubinstein *et al*. (2019); Mazgani *et al*. (2008); McMeekin *et al*. (2015); Julius *et al*. (2013); Makker *et al*. (2013); and ZoptEC study).[15-21] These comparisons include an inverse probability treatment weighting (IPTW) ITC between GARNET and the ZoptEC trial[15, 16] and a series of matching-adjusted indirect comparisons (MAICs) between GARNET and the remaining 5 studies included from the SLR (see CS B.2.7.2 and Appendix D.5.2 and D.5.3).

3.3.2.1 Methods of published studies included in the indirect comparisons

The study characteristics, clinical and demographic characteristics, and efficacy outcomes measures (see CS Appendix D.4.3 to D.4.6, D.5.2, and D.5.3 and summarised in ERG report Table 11: Baseline characteristics and efficacy outcomes in the studies included in the ITCs, and GARNET ITT population).

The ERG notes that the study characteristics, clinical and demographic characteristics, and efficacy outcomes measures appear to have some differences; those with potential relevance are:

- Study design: 2 RCTs and 4 non-RCTs.
- Sample size: Ranged from 17 to 255. McMeekin *et al*. (2015)[17] and ZoptEC[15, 16] provide a far greater sample size compared to the other studies.
- Clinical and demographic characteristics: Variance was observed in age; ethnicity, ECOG PS; FIGO stage; histology; and lines of therapy.
- Efficacy outcomes: Response rate was the main efficacy outcome for most of the studies except ZoptEC[15, 16], McMeekin *et al*. (2015)[17] and Julius *et al*. (2013),[20] where PFS or OS was their primary outcome.

- Definition of response rates, PFS and OS: The definitions were either not reported or varied between studies. Of relevance is the difference in PFS definition between ZoptEC[15, 16] and GARNET. Due to the differences in PFS between the two studies, a descriptive-only KM analysis was conducted to compare PFS between GARNET and ZoptEC;[15, 16] but an adjusted comparison of OS between ZoptEC[15, 16] and GARNET was conducted by the company.
- Tumour assessments: Studies used tumour assessments per RECIST v1.1 by blinded independent central review (BICR) or investigator[22] and RECIST v1 (for trials performed prior to 2009 when the RECIST v1.1 was published).

Owing to lack of data on patient characteristics and prognostic variables, and limitations in the study design from the published studies (see Table 11), the indirect treatment comparisons (ITCs) cannot account for any prognostic variable imbalances that are not reported, introducing an unknown level of bias. The ITCs were provided for completeness as supportive comparative efficacy evidence only and are used by the company in scenarios for the economic model. The ERG partly agrees with this.

The ERG considered the doxorubicin arm of ZoptEC[15, 16] a potential primary comparative effectiveness evidence alongside UK RWE study. The baseline characteristics of patients (excluding: ethnicity, ECOG PS, and FIGO stage) (see Table 11 and Clarification question A17, Table 14), setting and data collection methods were similar between GARNET and ZoptEC.[15, 16] There were differences in the presentation of information on stage of endometrial cancer (ZoptEC included an additional stage – “metastatic disease”), definition of PFS and timings of re-evaluation for response between GARNET and ZoptEC.[15, 16] Some of the differences in definition and baseline characteristics were accounted for by the choice of ITC method – inverse-probability weighted (IPTW) and excluding patients before the indirect comparison was conducted (see CS Appendix D.5.2, Table 44). In addition, relative to the studies included in the ITCs, individual patient-

level data (IPD) on ZoptEC large patient sample were available, thus, allowing the GARNET population to be matched with ZoptEC[15, 16] populations as closely as possible, minimising the heterogeneity between the two study populations, and resulting in more robust comparisons. The number of lines of prior anti-cancer treatment and tumour grade (key prognostic variables) were missing in the ZoptEC trial,[15, 16] which may impact the robustness of the study.

At the check point meeting, the company highlighted that because doxorubicin monotherapy is captured in the UK RWE study it was not necessary to include the ZoptEC trial[15, 16] as a primary comparator. The ERG notes that a comparative analysis to verify the similarities between the efficacy outcomes of the pegylated liposomal doxorubicin (PLD) or doxorubicin monotherapy in UK RWEGARNET-like cohort versus ZoptEC[15, 16] was not provided by the company.

Information on individual treatment regimens (including from PLD monotherapy) in the UK RWE GARNET-like cohort was provided by the company in response to clarification questions A3 and A9. Data on doxorubicin was not provided, as the company only presented information on treatments prescribed to ≥5% of patients in the UK RWE study GARNET-like population. The ERG found several differences in the demographic and clinical baseline characteristics between the UK RWE GARNET-like (PLD monotherapy) cohort and the doxorubicin arm of ZoptEC[15, 16] for the following characteristics: age (younger population in ZoptEC); ethnicity (ZoptEC had higher proportion of white ethnicity); ECOG PS (ZoptEC had higher proportion of patients in ECOG status 0 and 1, and about half of the GARNET like UK RWE (PLD monotherapy) population had their ECOG status unknown); FIGO stage (GARNET like UK RWE (PLD monotherapy) population had more advanced disease); and histology (Zoptec had grater endometroid disease) (see Table 11 below). It is unclear how these differences might affect baseline prognosis at the start of the second-line treatment for both groups, although many of the above differences may suggest less aggressive disease among the ZoptEC[15, 16] population. Further work on the comparative analysis has been conducted by the ERG (see ERG report section 3.5).

Besides ZoptEC,[15, 16] the ERG considered McMeekin *et al*. (2015)[17] (an RCT which provides evidence for doxorubicin or paclitaxel monotherapy) a reasonably robust study as it also had more information on inclusion/exclusion criteria, patient characteristics and prognostic data with large sample size relative to other studies included in the ITCs. However, the ERG notes that there were differences in the baseline characteristics of patients (including: ethnicity and histology) between the McMeekin *et al*. (2015) study[17] and GARNET trial. Also, the classification of patient's performance status differed between GARNET and McMeekin *et al*. (2015),[17] with the use of widely accepted ECOG status[24] and Karnofsky Performance Status (KPS),[25] respectively. The company matched KPS scale in McMeekin *et al*. (2015)[17] to ECOG status scale to align the performance measure across studies in this submission (see CS Appendix D.4.3, Table 19); however, KPS 90, 80, 70 and 60 were mismatched to their respective ECOG status. The ERG matched the performance scales (see Table 11 below) using the guidance provided by the ECOG-ACRIN Cancer Research Group.[26]

Some key prognostic variables were missing in the McMeekin *et al*. (2015) study,[17] including: FIGO stage, prior surgery, and number of lines of prior anti-cancer treatment, which may impact the robustness of the study. In addition, the IPDs were not available for McMeekin *et al*. (2015),[17] thus matching the study population with GARNET may lead to less robust comparisons compared to ZoptEC,[15, 16] consequently limiting it as a potential primary comparative efficacy evidence.

[redacted]Table 11: Baseline characteristics and efficacy outcomes in the published studies included in the ITCs, RWEQ and GARNET ITT population

Trial	GARNET ITT population (N=129)	GARNET-like UK RWE (RWEQ) cohort (N[redacted]	GARNET-like UK RWE (RWEQ) - PLD monother	Rubinstein *et al*. (2019) (N=20) [18]	Mazgani *et al*. (2008) (N=31) [19]	McMeekin *et al*. (2015) (N=248)* [17]	ZoptEC (N=255) [15, 16]	Julius *et al*. (2013) (N= 60) [20]**	Makker *et al*. (2013) (N= 17) [21]

			apy cohort (N=[redacted])						
Study design	Phase I open-label, single-arm (only Part 2B, Cohort A1 of interest)	Retrospective observational study	Retrospective observational study	Retrospective review of medical records of patients	Retrospective review of medical records of patients	Phase III open-label RCT	Phase III open-label RCT	Retrospective review of medical records of patients	Retrospective review of medical records of patients
Intervention	Dostarlimab	Basket of chemotherapy	PLD	Carboplatin + paclitaxel	Carboplatin + paclitaxel	Doxorubicin or paclitaxel monotherapy	Doxorubicin	PLD	Doxorubicin
Mean age, years (STD)	[redacted]	[redacted]	[redacted]	NR	NR	NR	63.8 (8.81)	66.8	NR
Median age, years (range)	[redacted]	[redacted]	[redacted]	67 (40 – 83)	NR	64 (33 – 88)	64 (28 – 87)	67 (34 – 87)	56 (36 – 78)
Age group n (%)									
<65 years	[redacted]	[redacted]	[redacted]	NR	NR	NR	136 (53.3)	NR	NR
65 to <75 years	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
≥ 65 years	[redacted]	[redacted]	[redacted]	NR	NR	NR	119 (46.7)	NR	NR
≥75 years	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Race n (%)									
White	[redacted]	[redacted]	[redacted]	NR	NR	213 (86)	240 (94.1)	44 (73.3)	16 (94.1)
Black	[redacted]	[redacted]	[redacted]	NR	NR	18 (7)	7 (2.7)	10 (16.7)	1 (5.9)

Asian	[redacted]	[redacted]	[redacted]	NR	NR	5 (2)	5 (2.0)	NR	NR
Other[a]	[redacted]	[redacted]	[redacted]	NR	NR	12 (5)	3 (1.2)	NR	NR
Unknown[b]	[redacted]	[redacted]	[redacted]	NR	NR	NR	0 (0.0	NR	NR
Performance status, n (%)	Study entry	Registry diagnosis	Registry diagnosis						
ECOG 0 (KPS 90-100)	[redacted]	[redacted]	[redacted]	NR	NR	165 (66.5)[c]	125 (49.0)	NR	NR
ECOG 1 (KPS 70-80)	[redacted]	[redacted]	[redacted]	NR	NR	80 (32.3)[c]	118 (46.3)	NR	NR
ECOG 2 (KPS (50-60)	[redacted]	[redacted]	[redacted]	NR	NR	2 (0.8)[c]	11 (4.3)	NR	NR
Not recorded	[redacted]	[redacted]	[redacted]	NR	NR	1 (0.4)[c]	1 (0.4)	NR	NR
Histology at diagnosis, n (%)									
Endometrioid	[redacted]	[redacted]	[redacted]	3 (15)	19 (61)	138 (55.6)	164 (64.3)	NR	5 (29.4)
Non-Endometrioid	[redacted]	[redacted]	[redacted]	17 (85)	12 (39)	109 (44.0)	91 (35.7)	NR	12 (70.6)
Missing	[redacted]	[redacted]	[redacted]	NR	NR	1 (0.4)	NR	NR	NR
FIGO stage[d], n (%)									
I	[redacted]	[redacted]	[redacted]	5 (25.0)	NR	NR	NR	NR	NR
II	[redacted]	[redacted]	[redacted]	3 (15.0)	NR	NR	NR	NR	NR
III	[redacted]	[redacted]	[redacted]	7 (35.0)	NR	NR	NR	NR	3 (17.6)
IV	[redacted]	[redacted]	[redacted]	5 (25.0)	NR	NR	NR	NR	14 (82.4)
Unknown	[redacted]	[redacted]	[redacted]	0 (0)	NR	NR	NR	NR	NR
Advanced (FIGO III or IV)	[redacted]	[redacted]	[redacted]	NR	NR	NR	94 (36.9)	NR	NR

Metastatic	[redacted]	[redacted]	[redacted]	NR	NR	NR	90 (35.3)	NR	NR
Recurrent	[redacted]	[redacted]	[redacted]	NR	NR	NR	71 (27.8)	NR	NR
Grade of disease at diagnosis, n (%)									
Grade 1	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Grade 2	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Grade 3	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Grade 4	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Not assessable	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Missing	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Prior anticancer treatment, n (%)									
Any prior anti-cancer treatment	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Surgery	[redacted]	[redacted]	[redacted]	NR	NR	NR	222 (89.2)	NR	NR
Radiotherapy	[redacted]	[redacted]	[redacted]	NR	NR	NR	138 (55.4)	NR	NR
Prior adjuvant chemotherapy	[redacted]	[redacted]	[redacted]	NR	NR	140 (57.0)	92 (36.9)	NR	NR
Number of prior lines of therapy post advanced/recurrent diagnosis, n (%)									
1	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
2	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
3	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
≥4	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Median PFS (months) [e] (95% CI)	[redacted]	[redacted]	[redacted]	10.0 (2.0, 47.0)	Endometroid: 8.0 (5.02, 12.72)	4.0 (2.7, 4.3)	[redacted]	7.0 (NR)	2.1 (0.97, 2.7)

					Serous: 9.0 (3.59, 35.4)				
Median OS (months) (95% CI)	[redacted]	[redacted]	[redacted]	27.0 (6.0, 117.0)	Endometroid: 15.0 (9.13, 30.36) Serous: 26.0 (9.72, 71.4)	12.3 (10.7, 15.4)	10.8 (9.8, 12.6)	7.0 (NR)	5.8 (1.0, 15.0)

Footnotes: [a] Includes American Indian or Alaska Native. [b] Includes 'Not reported'. [c] McMeekin *et al.* (2015) reported Karnofsky performance status scale (100, 90, 80, 70, 60, NR), rather than ECOG PS. [d] FIGO: For the RWE study this is at registry diagnosis and for Rubinstein et al. (2019) this is at diagnosis. [e] PFS was estimated using time to next therapy (TTNT) as a proxy for RWEQ and RWEQ PLD monotherapy cohorts. ZoptEC baseline estimates N= 255 were provided in response to clarification question A17. *For McMeekin *et al*. 2015, the 248 sample relates to the comparator arm of interest (Paclitaxel or doxorubicin monotherapy). For McMeekin *et al*. 2015, PFS is calculated from efficacy set (N = 223). ** Only the 40mg/m^2 dose (standard clinical) of PLD has been used from Julius *et al.* (2013) in the Matched adjusted indirect comparison (MAICs): other doses have insufficient bases.
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; KPS: Karnofsky performance status; FIGO: International Federation of Gynaecology and Obstetrics; STD: standard deviation; PFS: Progression Free survival; OS: Overall Survival.

3.3.2.2 Results of published studies included in the indirect comparisons

The median PFS for the published studies included in the indirect comparisons ranged from 2.1 (95% CI 0.97, 2.7) months in the Makker *et al.* 2013 study (doxorubicin)[21] to 10.0 (95% CI 2.0, 47.0) months in the Rubinstein *et al.* 2019 trial (carboplatin plus paclitaxel).[18] The median OS for the studies included in the indirect comparisons ranged from 5.8 (95% CI 1.0, 15.0) months in the Makker *et al.* 2013 study (doxorubicin)[21] to 27.0 (95% CI 6.0, 117.0) months in the Rubinstein *et al.* 2019 trial carboplatin plus paclitaxel[18] (see Table 11). Only the studies which included carboplatin plus paclitaxel therapy[18, 19] reported longer PFS and OS than GARNET; however, the ERG highlights that the wide confidence intervals reported and small sample sizes in the studies lead to uncertainties regarding these results.

ERG points of critique: Overall, the ERG notes the limited information available and associated uncertainties from most of the published studies makes it difficult to draw any meaningful conclusions. In addition to the UK RWEGARNET-like cohort, the doxorubicin arm of the ZoptEC trial[15, 16] may offer a valuable comparator population as the setting, data collection methods and patient characteristics were relatively aligned to the GARNET trial.

Safety

From the relevant published studies identified in the clinical SLR and included in the ITCs, only the ZoptEC trial[15, 16] (doxorubicin monotherapy) and McMeekin *et al*. (2015)[17] (paclitaxel or doxorubicin monotherapy) study had recorded safety information. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).[27] The same NCI CTCAE version (version 4.03) was used in the GARNET and ZoptEC trial,[15, 16] while version 3.0 was used by McMeekin *et al*. (2015).[17] Table 12 below (reproduced from CS Table 41) shows a naïve comparison of the treatment-related TEAEs in GARNET, ZoptEC[15, 16]

and McMeekin *et al*. (2015).[17] Overall, [redacted] of patients in GARNET experienced any treatment-related TEAEs in comparison to 90% of patients in the McMeekin *et al.* (2015) study,[17] and 96.4% (nearly all) in the ZoptEC trial.[15, 16] Notable differences were also observed in the frequently of the type of individual treatment-related TEAEs (occurring in ≥5% of patients) between GARNET and ZoptEC[15, 16] (see CS Table 42). McMeekin *et al*. (2015)[17] reported treatment-related TEAEs occurring in ≥20% of patients. The ERG notes that only the ZoptEC trial[15, 16] reported raw AE data. Grade ≥3 TEAEs from the ZoptEC trial[15, 16] were included in the individual scenario analyses in the cost effectiveness evaluation.

ERG points of critique: Overall, the ERG notes due to the differences in trial protocols, the comparisons of safety information between studies should be approached with caution. Chemotherapy interventions appear to exhibit higher toxicity relative to dostarlimab; however, the lack of data from most of the published studies is associated with some uncertainties with regards to toxicity.

Table 12: Treatment-related TEAEs in GARNET, ZoptEC and McMeekin et al. (2015) (reproduced from CS Table 41)

Trial	GARNET ITT population (N=129)	ZoptEC (N=249)[15, 16]	McMeekin *et al.* (2015) (N=239)[17]
Intervention	Dostarlimab	Doxorubicin monotherapy	Paclitaxel *or* doxorubicin monotherapy
Any treatment-related TEAEs, n (%)	[redacted]	240 (96.4)	215 (90.0)
Any Grade ≥3 treatment related TEAEs, n (%)	[redacted]	NR	NR
Any treatment-related SAE, n (%)	[redacted]	NR	29 (12.0)

Abbreviations: ITT: intention-to-treat; NR: not reported; SAE: serious adverse event; SLR: systematic literature review; TEAE: treatment-emergent adverse event.

3.4 *Critique of the indirect comparison*

3.4.1 Company's approaches and general caveats for unanchored indirect comparison

The GARNET trial is a single-arm trial and did not include any comparators. It is necessary to derive estimates of relative effectiveness between dostarlimab and other treatments through unanchored indirect comparison. This means there is no shared common comparator (e.g. placebo) through which comparisons between dostarlimab and other comparators of interest can be 'calibrated' in some way using data from RCTs that preserve random allocation of treatments and balance known and unknown confounders between treatment arms within individual studies. Consequently, unanchored indirect comparison heavily relies on comprehensive identification and adjustment of all prognostic factors and effect modifiers. Even if this can be achieved, there is still risk of residual confounding caused by unknown confounders. Failure to account for major imbalance in prognostic factors and effect modifiers between treatment arms being compared will result in biased estimates, the accuracy of which is unknown. Where there is insufficient evidence that the degree of bias arising from imbalance in confounders remaining unaccounted for is acceptable, NICE Technical Support Document (TSD) 18 recommended that the findings "*should be heavily caveated by noting: the amount of bias (systematic error) in these estimates is unknown, is likely to be substantial, and could even exceed the magnitude of treatment effects which are being estimated*".[28]

In unanchored indirect comparisons, attempts are often made to generate 'adjusted' results using the individual patient data (IPD) available from an index study, which is usually the study for the technology of interest, or GARNET trial in this STA. The adjustments aim to predict what results might have been observed in the GARNET trial population if its distribution of prognostic factors and effect modifiers were similar to the patient population in the comparator study. Ideally the latter would include a representative 'target population' for whom the new technology is indicated, as the findings from the indirect comparison would reflect the expected clinical effectiveness in

the target population. Findings from unanchored indirect comparisons therefore need to be interpreted with the nature of the comparator population in mind.

As described in Section 3.3, the company identified various sources of data from their SLR in order to inform unanchored indirect comparisons between dostarlimab and relevant comparators. It is unclear if the inclusion and exclusion criteria applied in the feasibility assessment for indirect comparisons were specified post hoc. The ERG reviewed the company's stated reasons for excluding or including individual studies for the indirect comparisons and considered them reasonable.

Individual studies/datasets used as comparators and corresponding indirect comparisons are summarised in Table 13. The company has chosen the matching-adjusted indirect comparison (MAIC) method for its primary indirect comparison with miscellaneous treatments used in clinical management in England using an REWQ dataset obtained from registry (described earlier in Section 3.3.1). Separate MAICs were also conducted for supportive indirect comparisons with other individual comparators using data from published trials in the literature.

The company justified the choice of MAIC over an alternative method of simulated treatment comparison (STC), described alongside MAIC in NICE Technical Support Document (TSD) 18, by suggesting that MAIC produces a marginal (population-level) treatment effect while STC produces only conditional (patient-level) treatment effects and citing a commentary[29] that mainly focused on anchored rather than unanchored indirect comparison (see CS Section B.2.7.1). The ERG is not entirely convinced by this, as the availability of IPD from GARNET means the predicted outcomes for individual patients can be used to construct population-level treatment effect.

Table 13: Comparator datasets and corresponding indirect comparisons included in the CS

Comparator dataset	Nature	Comparator(s) included in the dataset	Methods of indirect comparison used	Company's designation of the analysis	Findings informed economic model (CS Section 3.8.3)
GARNET-like RWE (RWEQ)	IPD from registry	Wide range of treatment regimens used in clinical practice in England	MAIC	Primary	Scenarios 6 & 7
ZoptEC	IPD from RCT	Doxorubicin monotherapy	IPTW	Supportive	Scenario 35
Makker et al. (2013)	Aggregated data from literature	Doxorubicin monotherapy	MAIC	Supportive	Scenarios 35, 36, 37, 38,39
McMeekin et al. (2015)	Aggregated data from literature	Doxorubicin monotherapy & paclitaxel monotherapy	MAIC	Supportive	Scenarios 36 & 39
Julius et al. (2013)	Aggregated data from literature	PLD	MAIC	Supportive	Scenario 38
Rubinstein et al. (2019)	Aggregated data from literature	Carboplatin plus paclitaxel	MAIC	Supportive	Scenario 40
Mazgani et al. (2008)	Aggregated data from literature	carboplatin plus paclitaxel	MAIC	Supportive	Scenario 41

Abbreviations: IPD: individual patient data; IPTW: inverse probability treatment weighting; MAIC: matching-adjusted indirect comparison; PLD: pegylated liposomal doxorubicin; RCT: randomised controlled trial

For the supportive indirect comparison between dostarlimab and doxorubicin monotherapy using individual patient data (IPD) obtained from the ZoptEC trial, the inverse probability treatment weighting (IPTW) method was used. The company justified the choice of IPTW in preference over propensity score matching (CS Appendix D, Section D.5.2) given the relatively small number of patients from each of the trial arms and that many patients may be eliminated in the matching process, which would impact

on interpretation of findings and reduce statistical power. ERG agrees with this. However, the rationale for choosing IPTW over STC method was not clearly stated. Given the challenges in clearly specifying the correct model for unanchored indirect comparison, there may be scope for using both methods (or adopting a doubly robust estimation methods described in TSD 18) to verify the validity of the analyses and robustness of the findings.

More detailed critique of individual unanchored indirect comparisons is provided below. The ERG focussed on GARNET versus (vs) clinical management using RWEQ and GARNET versus doxorubicin using ZoptEC as IPD for these two comparators were available to the company.

3.4.2 GARNET vs RWEQ (dostarlimab vs current clinical management)

3.4.2.1 Comparability of patient characteristics and datasets

In view of the scarcity of alternative data, the company sourced data from the NCRAS to create RWEQ cohort (see Section 3.3.1), which could potentially provide a suitable comparator dataset that represents current UK practice. Nevertheless, the difference in nature between GARNET (with data collected following a strict protocol in a trial setting) and RWEQ (with data retrospectively retrieved from registry collected during routine practice) poses substantial challenges in harmonising the two datasets and allowing a fair comparison to be made. Having examined the methods and findings of this unanchored indirect comparison, the ERG has strong reservation concerning its validity and the suitableness of the findings to support the base case.

As described in Section 3.3.1, there are major differences between GARNET and RWEQ, both in terms of the characteristics of patients included and in terms of the methods by which and settings in which the data were collected. Imbalance in patient characteristics (that are likely to be prognostic factors and effect modifiers) could be adjusted to some extent using appropriate statistical techniques. However, more concerning are systematic differences between the two cohorts of patients and related

data arising from methodological issues associated with data collection, case definition and selection (in particular, the necessary and yet complicated processes of reducing from 45,494 patients with EC diagnosis in the registry to the [redacted] patients included in the final RWEQ cohort). These systematic biases may not be easily recognised and cannot be 'adjusted away' by statistical means.

The major differences in patient characteristics between GARNET and RWEQ as described in Section 3.3.1.1 and Table 10 (e.g. a much higher proportion of patients with endometrioid disease in GARNET, [redacted] vs RWEQ, [redacted]) suggested a systematic difference in how patients were selected into the two cohorts, which raise some concerns regarding the comparability of the two datasets even after statistical adjustment.

In addition to the clear difference in baseline characteristics between GARNET and RWEQ, findings from company's analysis to verify prognostic factors also provide strong evidence that the two cohorts may have some fundamental differences. For example, the effect of tumour grade on OS was shown to be in opposite directions in separate Cox regression models for the two cohorts: HR (grade 3/4 vs 1/2) [redacted] (95% CI [redacted] to [redacted]) for the GARNET cohort compared to HR [redacted] (95% CI [redacted] to [redacted]) for the RWEQ cohort.

The marked differences between GARNET and RWEQ populations also raised the issue of whether the findings of the MAICs reflect what would be observed in the target population as defined in final scope. Data obtained from a registry are often considered more representative of patients encountered in clinical practice than patients recruited into clinical trials, and therefore using RWEQ as the comparator could be an advantage in the context of unanchored indirect comparison because the process of statistical adjustment aims to predict what outcome would look like if the GARNET trial population had a similar distribution of prognostic factors as seen in the comparator population. Nevertheless, representativeness of RWEQ here may be compromised by the many selection criteria retrospectively applied to the original RWE dataset and the imprecise methods for identifying recurrent cases to reach the highly selective RWEQ cohort. The resultant unanchored indirect comparison may therefore reflect findings that are

applicable only to a patient population that is difficult to define and not necessarily reflecting what would be expected in the target population.

In addition to the very limited prognostic factors taken into account in the MAICs, ERG noted several other issues in the process of selecting matching variables:

- Using ECOG PS at treatment initiation for GARNET ITT but using ECOG PS at registry (initial) diagnosis for RWEQ
- Modelling a very small number of patients with unknown histology and cancer grade as a separate category rather than treating them as missing data
- Lumping FIGO stage 3 and stage 4, which could be associated with quite different prognosis together in the analysis.

3.4.2.2 Methods of MAIC

In CS B.2.7.1, the company stated that "*The primary endpoint analysis considered in the UK RWE study MAIC utilised a Cox proportional hazards model, using weights obtained using the MAIC method.*" The company started with a list of potential prognostic factors identified from a 'targeted literature review' and subsequently selected by an expert panel (CS Appendix M); and then narrowed down the final matching variables by fitting two separate Cox proportional hazard models (one for GARNET and one for RWEQ) and retaining any variables that attained the level of significance p≤0.1 in at least one of the two datasets.

ERG considers the list generated by the expert panel (see Table 14) to be reasonably comprehensive but makes the following observations:

(1) Based on another systematic review conducted by the company (only a conference abstract was cited),[23] there is no evidence that MMR/MSI status has prognostic value among patients with recurrent or advanced EC receiving non-anti-PD-(L)1 therapy (CS Section B.2.3.2, page 50). However, as noted earlier in ERG report Section 3.3.1, the prevalence of dMMR/MSI-H differs between type I and type II EC, which in turn are

associated with various prognostic factors; therefore the differences in the distribution of MMR/MSI status between GARNET and RWEQ cohorts could still result in confounding and cause bias in the indirect comparison.

(2) The following potential prognostic factors were identified in the literature but were not selected by the expert panel:

- For good prognosis: absence of other systemic disease, smaller tumour size, resectability, longer disease-free interval, positive oestrogen and progesterone receptor, PTEN mutations.
- For poor prognosis: advanced EC (relative to recurrent EC), increased number of positive lymph nodes, substantial lymphovascular space invasion, desmoplasia in lymph nodes, extension of carcinoma into perinodal adipose tissue, distant recurrence, P53 gene mutation.

The rationale for excluding these potential prognostic factors was not described. ERG considers some of these factors such as disease-free interval and advanced vs recurrent EC to be potentially important.[30]

Table 14: Comparison of possible prognostic factors between those identified in the literature, selected company's expert panel and included in company's MAIC for GARNET vs RWEQ

Potential prognostic factors	Identified from company's targeted literature review	Selected by company's expert panel	Included in MAIC scenario 1	Included in MAIC scenario 2
Absence of other systemic disease	Yes	No	No	No
Race (Non-Hispanic White)	Yes	Yes	No	Yes
Increased Age	Yes	Yes	No	No
Smaller tumour size	Yes	No	No	No
Resectability / Prior surgery for study indication	Yes	Yes	No	Yes
Longer disease-free interval	Yes	No	No	No
Good Performance status	Yes	Yes	No	No
Advanced EC vs recurrent EC	Yes	No	No	No
FIGO	Yes*	Yes	No	Yes
Grade of disease at diagnosis	No	Yes	No	No
Number of prior platinum-based therapies	No	Yes	Yes	No
Histology: Serous & clear cell cancer	Yes	Yes	Yes	Yes
Increased number of positive lymph nodes	Yes	No	No	No
Substantial lymphovascular space invasion	Yes	No	No	No
Desmoplasia in lymph nodes	Yes	No	No	No
Extension of carcinoma into perinodal adipose tissue	Yes	No	No	No
Distant recurrence	Yes	No	No	No
Positive oestrogen and progesterone receptor	Yes	No	No	No
PTEN mutations	Yes	No	No	No
P53 gene mutation	Yes	No	No	No
MMR/MSI status	No	Yes	No	No

Footnote: *Described as: "Histology: FIGO grade 3"

The company constructed two scenarios (two final models): scenario 1 was based on prognostic factors identified by the expert panel; scenario 2 was based on variables identified from the above Cox proportional hazard model selection process. ERG is highly concerned with regard to whether the very limited matching variables included in these two scenarios enabled sufficient adjustment of imbalance in key prognostic factors between GARNET and RWEQ (see Table 14 below). No information on goodness of fit for the models or assessment of the magnitude of potential residual bias were presented.

As the company had access to IPD for both GARNET and RWEQ, it could have been possible for the company to carry out the MAIC by matching RWEQ to GARNET and created an adjusted RWEQ to be compared with unadjusted GARNET ITT as a sensitivity analysis and validity check.

Given the issues highlighted above related to both the datasets and the methods, ERG has strong reservations regarding the validity of the findings from these MAICs.

3.4.3 GARNET vs ZoptEC (dostarlimab vs doxorubicin)

3.4.3.1 Comparability of patient populations and datasets

As described in Section 3.3.2, the company sourced IPD from a ZoptEC trial identified in their SLR, which allow an unanchored indirect comparison to be carried out between dostarlimab and doxorubicin. Table 11 in Section 3.3.2 of this report and CS Appendix Table 40 shows that the baseline characteristics of patients were broadly similar between GARNET and ZoptEC, except for ethnicity, ECOG PS, and possible FIGO stage. Some of the differences were removed by excluding patients before indirect comparison was performed (see CS Appendix D.5.2, Table 44). Primarily, [redacted] patients with ECOG PS score 2 from ZoptEC trial were excluded as GARNET trial only included patients with ECOG PS score 0 or 1), and [redacted] patients in GARNET who had more than one prior line of platinum therapy were excluded because patients in ZoptEC only had one prior line of platinum therapy. These exclusions seem reasonable, but reduced the

sample sizes and thus statistical power for the indirect comparison. The company also excluded [redacted] patients with follow-up of longer than 36 months for doxorubicin group of the ZoptEC trial (CS Appendix D.5.2, Table 44). This exclusion might have introduced bias as the excluded patients would have had longer survival.

3.4.3.2 Methods for MAIC

The MAIC was carried out using a stabilised inverse probability of treatment weighting (IPTW) approach. This method was chosen in preference over propensity score matching (PSM) because of the relatively small sample sizes of the trials, as more patients may be eliminated during the PSM process. ERG agrees with this rationale, although it is not clear whether an alternative method of simulated treatment comparison was considered.

Overall, the methods for the MAIC using IPTW were described in good detail and were justified. The company stated that grade of tumour could not be included in matching due to violation of positivity assumption (CS Appendix D.5.2, page 117). This suggested patients with certain tumour grade rarely or never received either dostarlimab or doxorubicin, which would cause technical problems during the matching process, but further details were not provided. Analysis of potential impact of unmeasured confounding was provided and showed the findings of the MAIC were reasonably robust. The company did not perform IPTW for PFS, citing the differences in the definitions of PFS and the timepoints of tumour assessments between GARNET and ZoptEC (CS Section B.2.7.2). ERG believes such analysis could have been undertaken as a sensitivity analysis.

3.4.4 GARNET vs other comparators

3.4.4.1 Dostarlimab vs carboplatin + paclitaxel

Combination therapy of carboplatin plus paclitaxel is the most commonly used treatment regimen in the NHS for the target patient population, as reflected in RWEQ (used by [redacted]% of patients, see CS Table 14). The company identified two studies (Rubinstein *et al*.2019 and Mazgani *et al*. 2008) [18, 19] providing potentially relevant data for this comparator (see ERG report Section 3.3.2 and Table 11). ERG noted that the median PFS reported in these studies was [redacted] than that was reported for dostarlimab in GARNET before any adjustments were made. Both were retrospective studies of small sample sizes (n=20 and 31 respectively) and reported very limited information concerning prognostic factors and effect modifiers that would allow adjustments be made through MAICs (see Table 15 below). Because of these limitations, the findings from the MAICs were highly uncertain.

3.4.4.2 Dostarlimab vs paclitaxel monotherapy, doxorubicin monotherapy or pegylated liposomal doxorubicin (PLD) monotherapy

The company identified three additional studies in which relevant data for patients receiving paclitaxel or doxorubicin monotherapy (McMeekin et al. 2015), doxorubicin monotherapy (Makker et al. 2013) and PLD monotherapy (Julius et al. 2013) were available. Of these, only McMeekin et al. 2015 was a prospective trial with a relatively large sample size, but it also reported very limited information on prognostic factors and effect modifier to allow comprehensive adjustment (see Table 15 below). MAICs undertaken using the other two studies suffered from very small sample sizes (the effective sample sizes for GARNET also became much smaller during the matching process) and very limited adjustment and so the findings were also highly uncertain.

Table 15: Methodological features of MAICs presented in the CS

Source of comparator	Design	Therapy	Analysis	Matching variables	Validity assessment
RWEQ (n=[redacted])	Retrospective, UK registry	Clinical management	MAIC, scenario 1, vs GARNET (ESS=[redacted])	Histology Number of prior platinum-based therapies	Limited matching; possible violation of PH assumption; no assessment of residual bias
RWEQ (n=[redacted])	Retrospective, UK registry	Clinical management	MAIC, scenario 2, vs GARNET (ESS=[redacted])	Race/ethnicity Stage at diagnosis ECOG PS Histology Prior surgery	Limited matching; no assessment of residual bias
RWEQ ECOG PS ≤1 (n=[redacted])	Retrospective, UK registry	Clinical management	MAIC, scenario 1 (sensitivity analysis) vs GARNET (ESS=[redacted])	Histology Number of prior platinum-based therapies	Limited matching; possible violation of proportional hazard assumption
RWEQ ECOG PS ≤1 (n=[redacted])	Retrospective, UK registry	Clinical management	MAIC, scenario 2 (sensitivity analysis) vs GARNET (ESS=[redacted])	Race/ethnicity Stage at diagnosis ECOG PS Histology Prior surgery	No assessment of residual bias
ZoptEC (n=[redacted])	Trial	Doxorubicin	IPTW, main analysis, vs GARNET (n=[redacted]) OS only	Age Race ECOG PS Histology FIGO stage at baseline (Stage I/II versus Stage III/IV) Prior surgery	Tumour grade could not be adjusted due to violation of the positivity assumption; did not adjust for prior lines of therapy..

ZoptEC (n=[redacted]) [15, 16]	Trial	Doxorubicin	IPTW, sensitivity analysis, vs GARNET (n=129) OS only	Age Race ECOG PS Histology FIGO stage at baseline (Stage I/II versus Stage III/IV) Prior surgery	Tumour grade could not be adjusted due to violation of the positivity assumption; did not adjust for prior lines of therapy..
Rubinstein *et al*.2019 (n=20) [18]	Retrospective, single centre, USA	Carboplatin + paclitaxel	MAIC vs GARNET (ESS [redacted])	Histology	Very limited matching; violation of proportional hazard assumption for both PFS & OS
Mazgani *et al*. 2008 (n=31) [19]	Retrospective, single agency, Canada	Carboplatin + paclitaxel	MAIC vs GARNET (ESS [redacted])	Histology	Very limited matching; possible violation of proportional hazard assumption for PFS
McMeekin *et al*. 2015 (n=248) [17]	Trial	Paclitaxel (n=68) or doxorubicin (n=171)	MAIC, vs GARNET (ESS [redacted]) OS only	Race ECOG PS Histology	Very limited matching
Makker *et a*l. 2013 (n=17) [21]	Retrospective, single centre, USA	Doxorubicin	MAIC, vs GARNET (ESS=[redacted])	Race ECOG PS Histology	Very limited matching
Julius *et al*. 2013 (n=60) [20]	Retrospective, single centre, USA	PLD (n=41 for 40 mg/m^2)	MAIC, vs GARNET (ESS=[redacted]) OS only	Race	Very limited matching

Abbreviation: ESS: effective sample size

3.4.4.3 Dostarlimab vs hormone therapy

The company conducted a targeted literature review (CS Appendix L), but did not identify any studies that provide suitable data for the population of interest to enable an

indirect comparison. ERG checked the reasons stated by the company for study exclusion and considered them to be reasonable. ERG also undertook a separate search and did not identify any additional studies (see Section 3.1). Therefore, ERG agrees that there is currently a lack of data to allow reliable comparison be made between dostarlimab and hormone therapy in the population of interest.

3.4.5 Summary of critique of the indirect comparisons

As GARNET is a single arm trial without including a comparator, relative effectiveness between dostarlimab and comparator treatments has to be estimated through unanchored indirect comparisons, which are very susceptible to biases arising from differences in clinical and methodological features between different studies/data sources. The company identified two datasets with IPD and several other published studies with aggregate data, and undertook a suite of unanchored indirect comparisons using MAICs. However, ERG considered findings from all these MAICs to be highly uncertain due to a combination of the nature of the IPD datasets, limited information presented in published literature and issues related to MAIC methodology. The findings expressed as hazard ratios are summarised in Table 16, which should be interpreted with caveats highlighted below:

- The RWEQ cohort has very different characteristics compared with the GARNET population and the differences suggest RWEQ cohort was likely have more aggressive and advanced diseases and to be less fit compared with the GARNET trial population. Many issues related to the nature of the datasets and methods indicate that the MAICs comparing GARNET with RWEQ, which produced estimates more favourable for dostarlimab, are unlikely to be valid. ERG therefore prefers the unadjusted comparison over any of the MAICs for GARNET vs RWEQ, acknowledging that the estimates are likely to be biased in favour of dostarlimab.

- RWEQ included a basket of different treatments used in the UK clinical practice. A significant proportion of patients in the cohort were offered single agent

regimens that mean they were not fit for combination regimens, likely reflecting disease burden in stage 4 disease. They were more likely to be advanced stage at diagnosis than recurrent after successful initial management and therefore their overall outlook was likely worse from the start compared with GARNET trial population. It would be extremely difficult (if not impossible) to fully address the imbalance in known and unknown prognostic factors between the cohorts by statistical adjustment. An RCT of dostarlimab vs standard care might be the only way to obtain unbiased estimates.

- The IPTW unanchored indirect comparison between dostarlimab and doxorubicin using IPD from ZoptEC trial overcame some of the inherent limitations in registry data (i.e. RWEQ) that may be intractable. However, some important factors such as tumour grade and prior lines of therapy could not be matched.

- Most of the remaining MAICs based on published literature were limited by small sample sizes and very limited matching and therefore the level of uncertainty associated with the validity and representativeness of these findings is very high. ERG noted that (given similar comparator treatments, e.g. doxorubicin or PLD monotherapy), the estimated benefits for dostarlimab tend to be larger when the comparator data were sourced from retrospective studies than from prospective trials.

Table 16: Findings from company's MAICs, expressed as hazard ratios (HRs) for PFS and OS

Study/data set & design	Comparator	Analysis	ESS for GARNET	HR dostarlimab vs comparator	
				PFS	OS
RWEQ Retrospective (n=[redacted])	Clinical management	Unadjusted	129	Not estimated	[redacted]
RWEQ Retrospective (n=[redacted])	Clinical management	MAIC, scenario 1	[redacted]	Not estimated	[redacted]
RWEQ Retrospective (n=[redacted])	Clinical management	MAIC, scenario 2	[redacted]	Not estimated	[redacted]
ZoptEC Trial (n=[redacted])	Doxorubicin	IPTW, main analysis	[redacted]	Not estimated	[redacted]
ZoptEC Trial [15, 16] (n=[redacted])	Doxorubicin	IPTW, sensitivity analysis	129	Not estimated	[redacted]
Rubinstein *et al.*2019 [18] Retrospective (n=20)	Carboplatin + paclitaxel	MAIC	[redacted]	[redacted]	[redacted]
Mazgani *et al*. 2008 [19] Retrospective (n=31)	Carboplatin + paclitaxel	MAIC	[redacted]	[redacted]	[redacted]
McMeekin *et al*. 2015 Trial [17] (n=239)	Paclitaxel (n=68) or doxorubicin (n=171)	MAIC	[redacted]	No data	[redacted]
Makker *et al*. 2013 [21] Retrospective (n=17)	Doxorubicin	MAIC	[redacted]	[redacted]	[redacted]
Julius *et al*. 2013 [20] Retrospective (n=41)	PLD	MAIC	[redacted]	No data	[redacted]

3.5 *Additional work on clinical effectiveness undertaken by the ERG*

This section describes two pieces of additional work undertaken by the ERG to facilitate interpretation of clinical effectiveness evidence. The first work involves an unadjusted comparison of PFS and OS survival curves between the GARNET trial and other trials of PD-1 or PD-L1 inhibitors for recurrent or advanced EC to verify the company's claim that extended (flat) tails are a 'hallmark of I-O therapy' (CS page 146 and 199). The second work explored the possibility that data from trial settings tend to over-estimate treatment effectiveness compared with data obtained from real-world setting by making an unadjusted comparison of PFS and OS outcomes between ZoptEC trial (doxorubicin monotherapy) and the subset of RWEQ data for patients treated with PLD (pegylated liposomal doxorubicin) monotherapy provided by the company in response to ERG's clarification questions.

3.5.1 GARNET versus other trials of PD-1 or PD-L1 inhibitors

In the absence of longer-term data from GARNET, the ERG considered evidence from trials for other PD-1 or PD-L1 inhibitors with longer follow-up periods and reported survival curves in post platinum, second line treatment of recurrent or advanced EC, and conducted a rapid analysis to assess if the shape of the survival curves from GARNET are truly unique or characteristic of I-O therapy. The ERG is aware that the shape of survival curves and the extent and positioning of flat tails is dependent on many factors, not only class of intervention (e.g. PD-1 or PD-L1 inhibitors), but including maturity of data (proportion of participants experiencing the event) which in turn is influenced by the length of follow up, the severity of the disease and the effect on event rate of interventions, and heterogeneity of the included population. Table 17 summarises the study characteristics and survival outcomes for other PD-1 or PD-L1 targeted interventions.

Makker *et al*. 2019 and 2020[31, 32] is a single arm phase 2 study of pembrolizumab plus lenvatinib (from an interim analysis and more mature analysis, respectively), with longer study follow-up than GARNET, and patient characteristics similar to GARNET. Figure 4 shows PFS and OS KM plots for Makker *et al*. (2019 and 2020) study[31, 32] versus GARNET. More mature data from Makker reduces the flat tail and introduces events that move the PFS KM plot more toward baseline. It seems possible that more mature data for GARNET might have the same PFS and OS pattern as the Makker et al. (2020) study.[32]

Ott *et al*. (2017)[33] is a single arm phase 1 study of pembrolizumab, with longer study follow-up than GARNET, smaller sample size and less comparable patient characteristics (such as age) to GARNET. Figure 5 shows PFS and OS KM plots for Ott *et al*. (2017)[33] study versus GARNET. The shapes of the plots are similar; however, the faster rate of events in Ott *et al*. (2017)[33] means the flat tail gets closer to zero survival and becomes less influential.

Overall, the rapid analyses conducted by the ERG showed that the extended tail in I-O therapies is likely subdued when follow up is sufficiently extended. This is supported by further exploratory analyses of survival data from trials of check point drugs in non-small cell lung cancer (NLSCLC) shown in ERG Appendix 9.2.

Table 17: Study characteristics and survival outcomes for other PD or PD-L targeted interventions

Author	• **Study design** • **Follow-up** • **Prior platinum therapy** • **Sample size** • **Age (mean), years** • **FIGO stage** • **ECOG PS**	**Intervention**	• **Definition of PFS** • **PFS (months)**	**OS (months)**
Makker *et al*. (2020)[32]	• Ongoing phase 2 study • Median follow-up of 18.7 months	Oral lenvatinib 20 mg once daily plus 200 mg intravenous	• Median PFS: 7.4	Median OS: 16.7

	• Yes • 108 patients • 65.1 • FIGO stage: 1 (n =12), 2 (n =19), 3 (n =24), not reported (n =53) • ECOG PS: 0 (n =53), 1 (n =55)	pembrolizumab once every 3 weeks, in 3-week cycles.		
Makker *et al*. (2019)[31]	• Ongoing phase 2 study • Median study follow-up was 13·3 months • Yes • 53 patients • 64 • FIGO stage: 1 (n =5), 2 (n =11), 3 (n =6), not reported (n = 31) • ECOG PS: 0 (n =20), 1 (n =33)	Oral lenvatinib 20 mg daily plus 200 mg intravenous pembrolizumab once every 3 weeks.	• Defined as the time from first study dose to date of first documented disease progression or death, whichever occurred first • With a median follow-up for progression free survival of 7·7 months • 27 (51%) patients had disease progression or had died, median progression-free survival was 7·4 months (95% CI 5·0 to not estimable).	NR
Ott *et al*. (2017)[33]	• Multicohort phase Ib KEYNOTE-028 trial • Median follow-up duration was 76.2 weeks • Yes (mostly n =25) • 24 patients • 67 • FIGO stage: NR • ECOG PS: 0 (n =7), 1 (n =16), not reported (n=1)	Pembrolizumab ,10 mg/kg every 2 weeks for up to 24 months or until progression or unacceptable toxicity.	• PFS defined as time from allocation to the first documented disease progression according to RECIST (version 1.1) or death resulting from any cause. • Median PFS: 1.8 (95% CI, 1.6 -2.7)	Median OS: 4.3 to not reached. 6-months OS rates: 67% 12-months OS rates: 51%

			• 6-months PFS rates: 19% • 12-months PFS rates: 14.3%	

Figure 4: PFS and OS KM plots for Makker et al. (2019 and 2020) study versus GARNET

Figure 5: PFS and OS KM plots for Ott et al. (2017) study versus GARNET

3.5.2 [redacted] (doxorubicin arm)

In addition to the differences in the patient characteristics between RWEQ PLD and ZoptEC (doxorubicin arm)[15, 16] described by the ERG in report section 3.3.2.1), the ERG

conducted analyses to assess the potential difference in effectiveness outcomes between RWEQ PLD and ZoptEC (doxorubicin arm)[15, 16] (Figure 6 and Figure 7 below). *Note: ZoptEC n=[redacted] populations represent the derived main analysis set used for the PFS and OS ITCs*. Given the broad equivalence between doxorubicin and PLD, better outcomes observed for doxorubicin monotherapy in ZoptEC [15, 16] compared with PLD monotherapy in RWEQ would suggest potential under-estimation of treatment effects of chemotherapy in real-world setting compared with those obtained in a trial setting. This in turn would lend support to the possibility that the use of RWEQ might have resulted in an under-estimation (of a similar magnitude) of the effects of the basket of therapies used in real-life clinical practice, compared with if they had been evaluated in a trial setting that is more comparable to the GARNET.

Figure 6: PFS for RWEQ PLD monotherapy versus ZoptEC (doxorubicin arm)

Figure 7: OS for RWEQ PLD monotherapy versus ZoptEC (doxorubicin arm)

3.6 *Conclusions of the clinical effectiveness section*

The CS presents evidence from GARNET, a Phase 1, single-arm, open-label study of dostarlimab conducted in 9 countries (including 9 centres in UK).

A total of 129 patients received any amount of dostarlimab, and this population was used in the base case cost-effectiveness analyses. Clinical outcomes suggested a potential for positive response to treatment with dostarlimab; however, the pivotal trial of dostarlimab has a short follow-up time frame and some outcomes do not have enough data to be fully informed. In the absence of a comparator group, it is unclear whether there is a meaningful improvement over established clinical management.

Evidence for the comparator (basket of chemotherapies) was taken from the RWEQ cohort of the UK RWE study funded by GSK. The RWEQ cohort included [redacted] patients. Supportive indirect comparisons with other individual comparators were also conducted using data from published studies in the literature.

Overall, the ERG's key concerns in the clinical effectiveness are:
The magnitude of the benefit of dostarlimab over treatment with chemotherapy and hormone therapy is uncertain. The main source of evidence was a phase I trial, with immature data and no comparator arm, and comparison with chemotherapy was from unanchored indirect treatment comparisons.

There are uncertainties with regard to whether the procedures for retrospectively selecting patients into the final RWEQ cohort in the UK RWE study produced a patient cohort that is representative of the target patient population in the UK. There are major differences in setting, patient characteristics and case definitions between the GARNET trial population and the RWEQ cohort. The major differences between the GARNET trial population and the RWEQ cohort remained after the matching process in the primary MAICs. Limited prognostic factors could be adjusted for in the supportive MAICs using other sources of comparator evidence. Estimates of relative effectiveness between dostarlimab and comparator treatments obtained from both unadjusted comparisons and the MAICs presented in the CS are highly uncertain and are likely to be biased in favour of dostarlimab.

4 COST EFFECTIVENESS

4.1 *ERG comment on company's review of cost-effectiveness evidence*

4.2 *The company presents an extensive systematic literature review of economic evaluations, quality of life values and resource use. This appears to have been competently conducted, is well summarised but is of limited use given the disease area and in particular the lack of relevant quality of life studies.* *Summary of the company's submitted economic evaluation*

4.2.1 NICE reference case checklist

Table 18: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes.
Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes, cost utility analysis. The company base case makes a naïve comparison between dostarlimab and a pooled real world data comparison. Scenarios that compare dostarlimab with individual treatments are also presented. A fully incremental analysis is not presented. The ERG thinks this is reasonable given the base case and that the individual treatments will be used for different groups of patients based upon their fitness.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. 40 years.

Element of health technology assessment	Reference case	ERG comment on company's submission
Synthesis of evidence on health effects	Based on systematic review	The base case compares dostarlimab with a real world basket of treatments. The scenarios around individual treatments are rooted in a systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes. EQ-5D-5L cross walked to EQ-5D-3L and valued using the standard UK social tariff.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes. The standard UK social tariff.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes. The standard UK social tariff.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company presents a partitioned survival analysis with the usual three main health states of progression free survival (PFS), post progression survival (PPS) and dead. This uses a Markov model with a 3 week cycle to match the dostarlimab infusion

frequency. The distribution of patients between the three main health states is determined by the overall survival (OS) curve and the PFS curve.

The OS and PFS curves for dostarlimab are derived by fitting parameterized curves to the GARNET Kaplan Meier (KM) OS and PFS data. For the comparator arm the OS and PFS curves are estimated by fitting parameterized curves to the RWEQ KM OS and Time to Next Treatment (TTNT) data, TTNT being used as a proxy for PFS due to progression data not being available for the RWEQ.

The time on treatment curves are estimated by fitting parameterized curves to the KM Time to Treatment Discontinuation (TTD) data of GARNET and the RWEQ.

Unusually, and in part justified by the approach of TA571, the company imposes stopping rules for dostarlimab, assuming that at [redacted] all but [redacted] of patients stop treatment and at [redacted] all patients stop treatment.

Due to the dostarlimab treatment stopping rules the company applies a waning treatment effect to the dostarlimab OS and PFS curves. The company assumes that the treatment effect is retained for [redacted] after stopping dostarlimab, so the extrapolated dostarlimab OS and PFS curves are unaffected by treatment cessation. After this it takes another [redacted] for all the treatment effect to be lost, with the dostarlimab OS and PFS efficacy being equalized with the contemporaneous RWEQ OS and PFS efficacy.

As the ERG found some of the company submission difficult to follow and lacking some detail, the detail of the company modelling is presented in sections:

4.2.6 from page 100100: treatment effects and extrapolation;

4.2.7 from page 115115: health related quality of life; and

4.2.8 from page 116116: resource use and costs.

While many readers will prefer to skip forward to section 4.3 on page 120120 which presents the main ERG critique of the company economic modelling, the graphical

presentation of the company curves and expert responses of section 4.2.6 may be more easily digestible than those of the company submission.

4.2.3 Population

The population reflects the scope but is subject to the concerns raised about the naïve comparison in the clinical review section.

- For dostarlimab the efficacy estimates are drawn from the GARNET population.
- For the comparator arm the efficacy estimates are drawn from the RWEQ population, pooled across the various chemotherapy regimens in the RWEQ data set.

4.2.4 Interventions and comparators

For the company base case the company compares dostarlimab with the basket of chemotherapy treatments of the RWEQ data set, though for costing only includes treatments which comprised more than 5% of the RWEQ data set. For costing it is also assumed that some comparator arm patients will receive hormone therapy.

4.2.5 Perspective, time horizon and discounting

The perspective and discounting is as per the NICE reference case. The time horizon is 40 years, which is sufficient to capture the extrapolated OS curves.

4.2.6 Treatment effectiveness and extrapolation

Unusually, given the assumptions about dostarlimab stopping rules and treatment waning, the OS and PFS modelling is best understood by reviewing the TTD curves first, followed by the comparator RWEQ OS and PFS curves. The dostarlimab OS and PFS curves estimated from GARNET can then be presented, followed by a presentation of how the treatment stopping rules and waning to RWEQ effectiveness affects these curves.

4.2.6.1 TTD Curve: dostarlimab

The company states that it fits a range of parameterized curves to the ITT (N=129) GARNET TTD KM data.

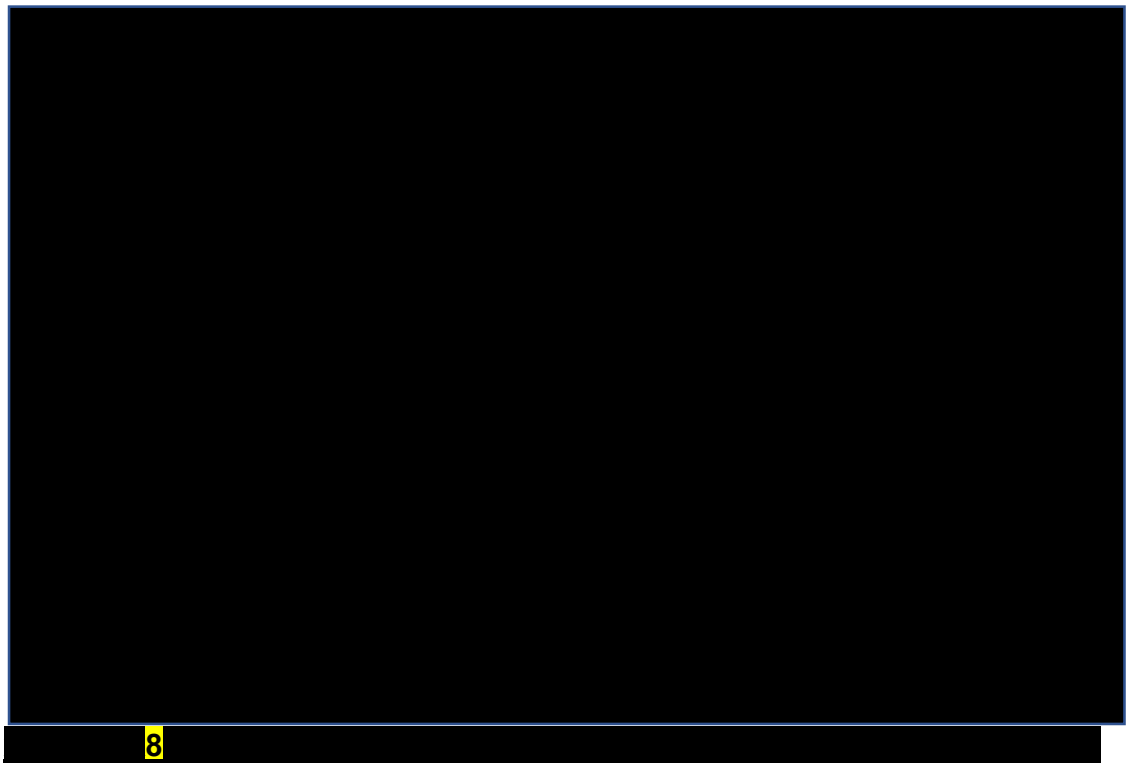


Table 19: Company GARNET TTD parameterised curves information criteria

	EXPO	WEIB	GOMP	LOGN	LOGL	GAMM	GGAM	SPL1	SPL2
AIC									
BIC									
Sum									

The information criteria minima are highlighted in bold, with the company choice highlighted by a bold border. The company selects the log-logistic curve, stating that "*the Gompertz and the log-logistic models were considered to provide the best statistical fit*". The ERG notes that the Gompertz has better AIC and BIC than the log-logistic, with their combined total being somewhat below that of the log-logistic.

In GARNET the KM proportion remaining on treatment at [redacted] Despite this, and partly justified by the approach of TA571, the company assumes that at [redacted] all but [redacted] of patients will discontinue dostarlimab and that at [redacted] all patients will discontinue dostarlimab.

[redacted] 9

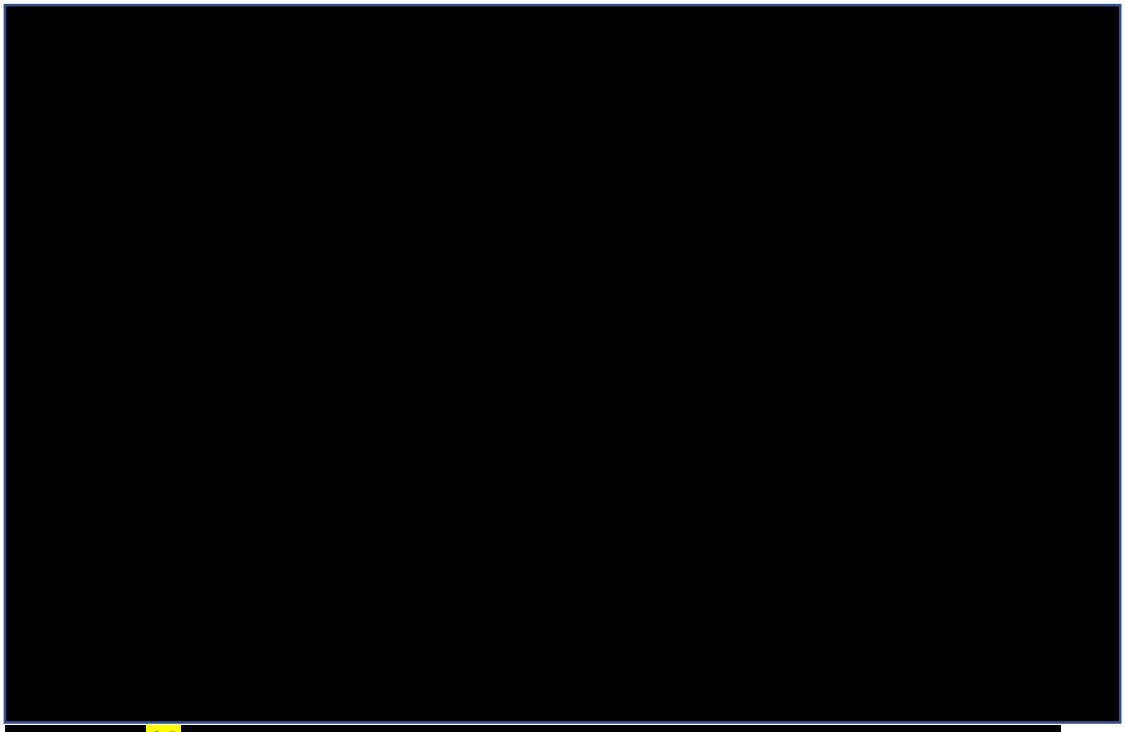
If the spline models are discounted as unnecessary due to long term extrapolations being unnecessary the Gompertz has the best information criteria. The reasoning behind the choice of the log-logistic is unclear. Within the company model the average time spent on treatment is [redacted] months if the log-logistic is applied and [redacted] months if the Gompertz is applied: a difference of [redacted].

The dostarlimab TTD curve of [redacted] is critical to the modelling. Most obviously, it determines the costs of dostarlimab within the model. But perhaps even more importantly it determines the OS and PFS curves in the dostarlimab arm. Given the discontinuations at year [redacted] the company assumes that the treatment effect of dostarlimab is retained in full for [redacted] year after this, but then wanes during years [redacted]

and [redacted] so that "*at* [redacted] *years … the efficacy associated with dostarlimab was assumed to be equal to the efficacy associated with current clinical management*".

4.2.6.2 TTD Curve: comparator RWEQ

While the comparator RWEQ TTD curve does not affect anything in the dostarlimab arm, it's derivation is presented here so as to sit alongside that of dostarlimab.



[redacted] 10

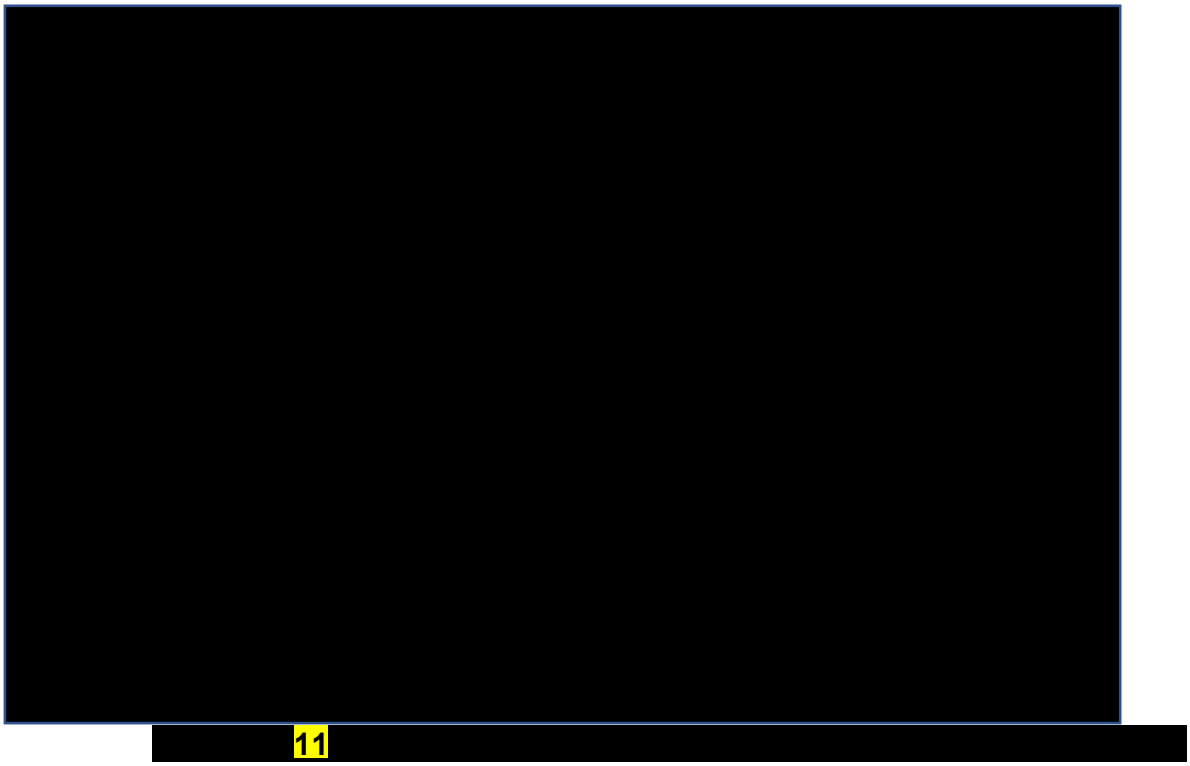
Table 20: Company RWEQ TTD parameterised curves information criteria

	EXPO	WEIB	GOMP	LOGN	LOGL	GAMM	GGAM
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The company states "*the generalised gamma and gamma model provided the best fit to the observed ToT data from the UK RWE study. The generalised gamma model was therefore included in the base case*". Despite the gamma having a lower sum of

information criteria and perhaps being the more natural choice, it can be noted that the modelled discounted time on treatment is virtually identical for the two curves.

4.2.6.3 OS curve: comparator RWEQ



At 65 months, the parameterised curves have broadly grouped into those suggesting around 5% survival, the log-normal, log-logistic, Gompertz and generalised gamma, and those that suggest minimal survival, the exponential, Weibull and gamma.

Table 21: Company RWEQ OS parameterised curves information criteria

	EXPO	WEIB	GOMP	LOGN	LOGL	GAMM	GGAM
AIC							
BIC							
Sum							

The company noted that both the log-logistic and the log-normal has good information criteria, but that both tended to underestimate overall survival when compared to the

company clinical expert responses. The company selected the log-logistic due to its information criteria and it predicting marginally higher survival than the log-normal. The mean survival estimates of the company experts were more than double that of the log-logistic curve at 5 years, and roughly treble those of the log-logistic curve at 10, 15 and 20 years, the individual responses being the small back dots and their average the larger diamonds. It is unclear why no expert responses were elicited for 3 years for RWEQ, particularly given its shorter anticipated OS and PFS compared to dostarlimab.

12

4.2.6.4 PFS curve: comparator RWEQ

Due to the RWEQ data not recording progression the company uses time to next treatment (TTNT) as a proxy. The company notes that this may bias the analysis against dostarlimab because it is likely that progression will occur before TTNT.

13

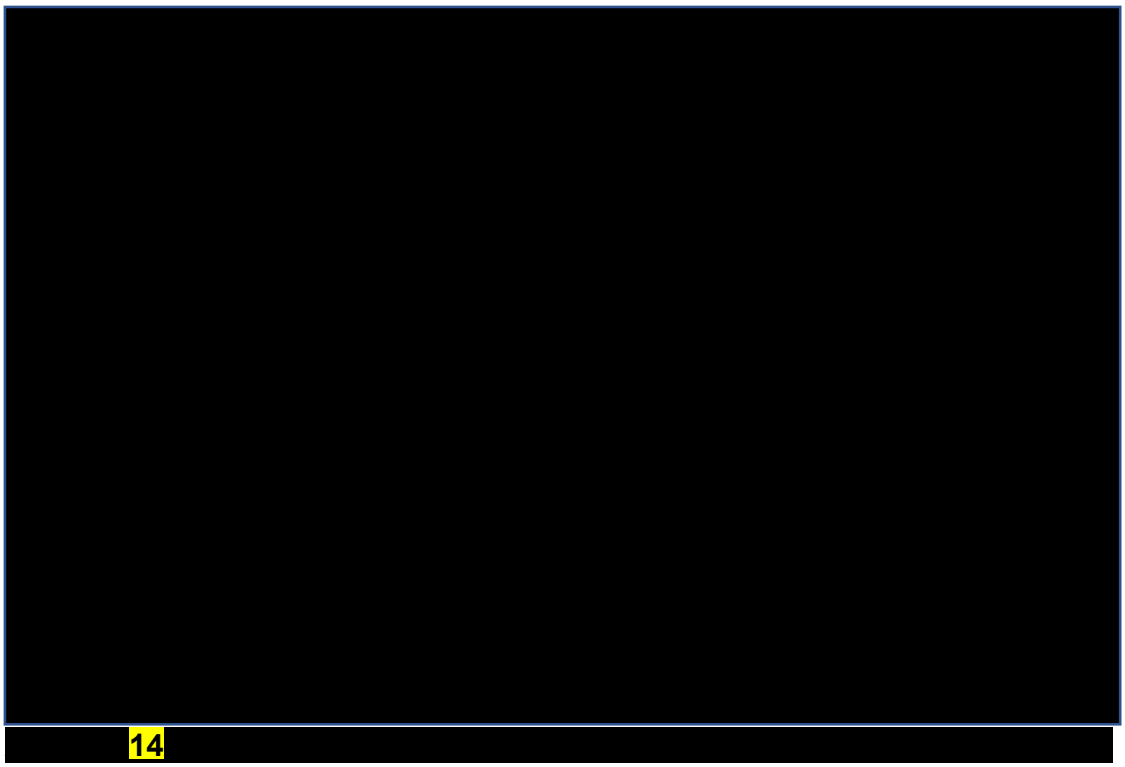
It may be questionable whether any of the TTNT parameterized curves fits the RWEQ KM data particularly well. The curves all tend to lie above the KM S(t) curve from month 9 to 24 and then tend to fall below it.

Table 22: Company RWEQ TTNT parameterised curves information criteria

	EXPO	WEIB	GOMP	LOGN	LOGL	GAMM	GGAM
AIC							
BIC							
Sum							

The company notes that the RWEQ TTNT extrapolation is less sensitive to the choice of curve. Based upon the information criteria the company selected the log-logistic, this also estimating slightly higher percentages than the other curves. But similar to the RWEQ OS curve, the company noted that the mean survival estimates of the company

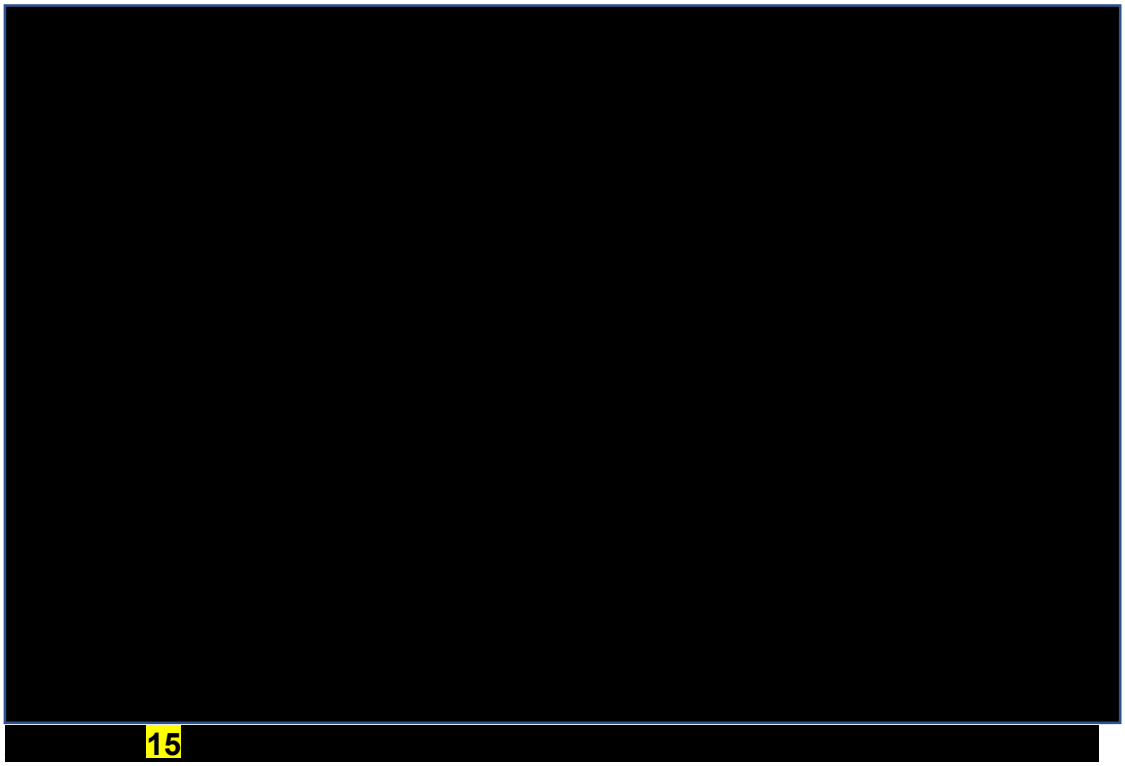
experts were roughly treble that of the log-logistic curve at 5 years, and more than treble those of the log-logistic curve at 10, 15 and 20 years.



14

4.2.6.5 OS curve: dostarlimab

The company fits the same set of parameterized curves to the GARNET OS KM data as it does the TTD data.



15

Table 23: Company GARNET OS parameterised curves information criteria

	EXPO	WEIB	GOMP	LOGN	LOGL	GAMM	GGAM	SPL1	SPL2
AIC									
BIC									
Sum									

16

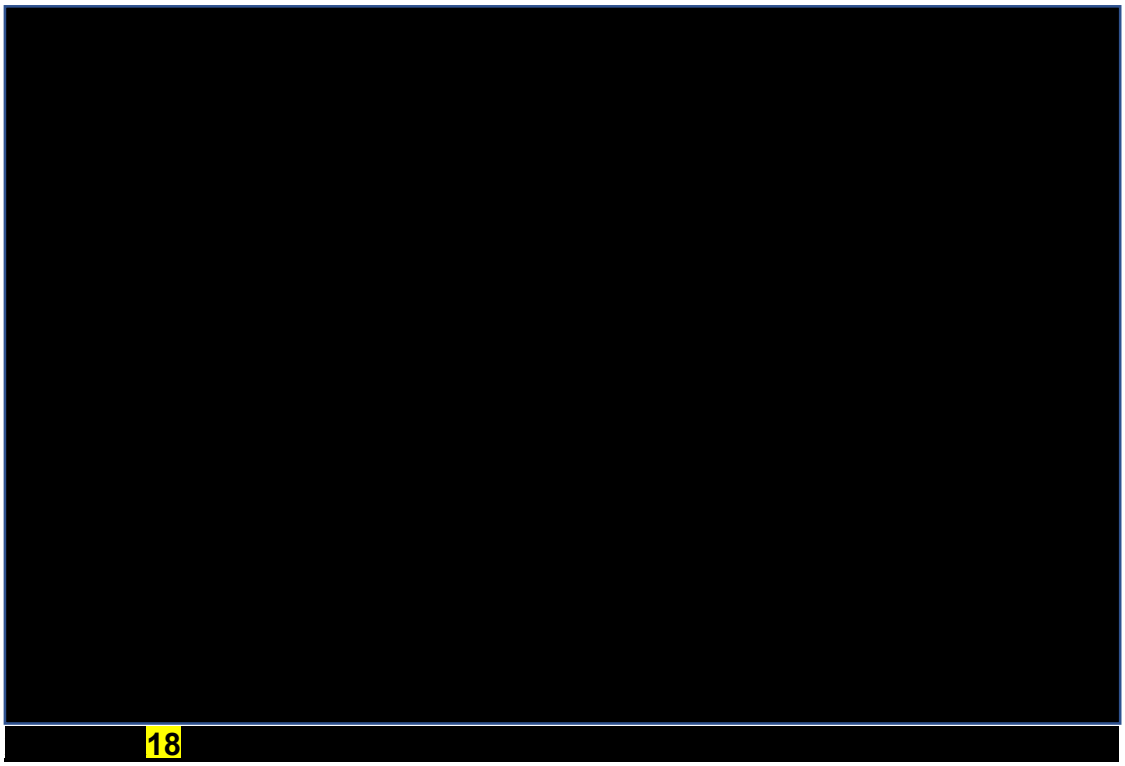
The unadjusted curves diverge markedly after two years. The company experts' estimates of the probable survival at 3, 5, 10, 15 and 20 years also show a large spread. The company base case adjusted the OS curves for treatment waning between year [redacted] and year [redacted], due to the treatment cessation assumption at year [redacted].

17

Despite the log-normal having a similar AIC and a superior BIC to the generalised gamma, the company selected the generalised gamma due to its waned curve conforming more closely to the means prediction of the company experts. The log-normal curve was deemed to provide too low an estimate of overall survival for dostarlimab.

4.2.6.6 PFS curve: dostarlimab

The parameterized curves fitted to the GARNET PFS KM data is shown below.



18

Table 24: Company GARNET PFS parameterised curves information criteria

	EXPO	WEIB	GOMP	LOGN	LOGL	GAMM	GGAM	SPL1	SPL2
AIC									
BIC									
Sum									

19

Adjusting the PFS curves for treatment waning between years [redacted] and [redacted] due to treatment cessation at year [redacted] has less effect upon the dostarlimab PFS curves.

20

The company identified the generalised gamma and the Gompertz as having the best fit to the Kaplan Meier data, based partly on expert opinion. But given the dostarlimab OS curve the company selected the log-normal PFS curve as a more conservative and better aligned PFS curve.

4.2.6.7 Modelled curves

The final set of curves that are applied in the company base case are presented in Xxxxxxx21 and Xxxxxxx22.

21

Even given the major adjustment to the dostarlimab OS curve there is still a considerable divergence between the OS curve and the PFS curve. The modelling consequently estimates that in the dostarlimab arm a considerable amount of overall survival is spent in the PPS health state after progression has occurred. A similar picture emerges in terms of the PFS curve and the TTD curve, the modelling estimating that much of the time spent in PFS occurs after cessation of treatment.

22

For the RWEQ comparator the OS and PFS curves are much more closely aligned and relatively little of overall survival is spent in the PPS health state after progression has occurred.

4.2.7 Health related quality of life

The company analyses the GARNET EQ-5D-5L data of the [redacted] patients reporting their baseline EQ-5D and at least one subsequent EQ-5D. The small number of patients reporting EQ-5D appears was due to EQ-5D data only being collected from study protocol 3. The EQ-5D-5L data was cross walked to EQ-5D-3L using the standard algorithm and evaluated using the UK social tariff. A range of models were explored. Generalised estimating equation (GEE) was used with patient identifiers to identify repeat sampling from individuals. The final company model included baseline quality of life, post progression survival (PPS) and being within 15 weeks of death, equivalent to 5 three week model cycles. An alternative model, Model 2, excluding the time to death variable was included as a scenario analysis.

Table 25: Company quality of life models

	Model 1	Model 2
Constant	[redacted]	[redacted]
Baseline	[redacted]	[redacted]
PPS	[redacted]	[redacted]
< 15 weeks to death	[redacted]	[redacted]

Given the mean baseline quality of life of [redacted] this resulted in the following quality of life values.

Table 26: Company quality of life values

	Model 1	Model 2
PFS	[redacted]	[redacted]
PFS and <15 weeks to death	[redacted]	[redacted]
PPS	[redacted]	[redacted]
PPS and < 15 weeks to death	[redacted]	[redacted]

A multiplicative age adjustment to these quality of life values was applied using the standard reference.

Note that the submission values were originally based upon [redacted] patients. The company has since updated this to the [redacted] patients.

4.2.8 Resources and costs

4.2.8.1 Dostarlimab drug and administration costs

Dostarlimab is initially administered every 3 weeks, but from the 5th administration the dose and treatment interval are both doubled. The original company submission included a [redacted] PAS. This has been increased to [redacted] at technical engagement. All costs and ICERs within this document reflect the increased [redacted] PAS. This results in the following costs by model cycle. The simple IV 1st infusion reference cost of £241 is applied to the first cycle, with subsequent administrations being costed using the £332 reference cost for subsequent administrations. This results in the following drug and administration costs by 3 week model cycle.

Table 27: Dostarlimab drug and administration costs per model cycle

	Cost	PAS	PAS inc.	Size mg	
Dostarlimab	£5,887	[redacted]	[redacted]	500	
	Dose mg	Days	Per cycle	Admin	Total
Dose Cycle 1	500	21	500	£241	[redacted]
Dose Cycles 2-4	500	21	500	£332	
Dose Cycles 5+	1000	42	500	£166	

4.2.8.2 RWEQ drug and administration costs

The company costs the individual treatments that comprise more than 5% of the RWEQ basket using the CMU EMIT database, and where this lacks entries the BNF. Combination therapies incur the Complex IV 1st administration £307 NHS reference cost. The company further assumes that 20% of patients will receive hormone therapy. A weighted average of the resulting costs is applied to the RWEQ TTD curve of the model. This results in the following costs per 3 week model cycle.

Table 28: RWEQ drug and administration costs per model cycle

	CARP	CPLD	PLDM	PACM	CARM	HORM	Average
Weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Drug costs	£37	£1,084	£1,069	£37	£15	£21	[redacted]
1st admin	£307	£181	£181	£723	£181	£0	
Subs admin	£496	£249	£249	£996	£249	£0	
CARP: carboplatin + paclitaxel, CPLD: carboplatin + PLD, PLDM: PLD monotherapy, PACM, paclitaxel monotherapy, CARM: carboplatin monotherapy, HORM: hormone therapy							

4.2.8.3 Ongoing monitoring costs

Ongoing monitoring costs are based upon expert opinion and costed using the usual NHS reference costs and PSSRU costs. Resource use, unit costs and total costs by health state are as below.

Table 29: Ongoing monitoring resource use and costs

	PFS On Tx	PFS Off Tx	PPS	Cost
OP Consultant Follow-Up visit	1.0	0.3	0.3	£176
Blood test	1.0	0.3	0.3	£3
CT scan	0.3	0.3	0.3	£97
Specialist Nurse	1.0	1.0	1.0	£50
GP visit	1.0	1.0	1.0	£39
GP Nurse visit	0.3	0.3	0.3	£48
Cost per 3 week cycle	£312	£186	£186	

4.2.8.4 Subsequent treatment costs

GARNET suggests that of those who have ceased dostarlimab treatment [redacted] received a subsequent treatment. The distribution of these between chemotherapy treatments is assumed to be as per the RWEQ arm; i.e. the RWEQ 2nd line treatment. The company further assumes that 10% will be radiotherapy and 5% hormone therapy, reducing the proportions of chemotherapy treatments to proportionately so that the treatment distribution sums to 100%; i.e. those who receive a subsequent treatment receive 1 subsequent treatment.

The RWEQ data suggests that after their 2nd line treatment [redacted] of patients received a subsequent treatment. But it appears that the RWEQ may not have collected radiotherapy data or hormone therapy data. The company adds an absolute 10% radiotherapy and 5% hormone therapy, resulting in a proportion receiving 3rd line treatment in the RWEQ arm of [redacted]. The distribution between the chemotherapy treatments is that of the 3rd line RWEQ data.

No administration costs are applied.

The duration of subsequent treatments is largely taken from the RWEQ data set, being [redacted] model cycles for 2nd line and [redacted] model cycles for 3rd line. The durations of radiotherapy and hormone therapy are taken from the literature.

The total cost is applied to the proportion falling out of PFS each cycle.

Table 30: Subsequent treatment costs

				Model cycles	
	DOST	RWEQ	Drug	2nd line	3rd line
Paclitaxel monotherapy	[redacted]	[redacted]	£37	[redacted]	[redacted]
Carboplatin monotherapy			£15		
PLD monotherapy			£1,069		
Carboplatin + PLD			£1,084		
Carboplatin + paclitaxel			£37		
Carboplatin + gemcitabine			£66		
Radiotherapy			£2,723	8.7	8.7
Hormone therapy			£21	4.6	4.6
Total Cost	£3,011	£2,883			

4.2.9 Adverse events

While clinically important, adverse events have relatively little effect upon the model outcomes and so the ERG does not present the detail of their cost and QALY calculations. In brief, for dostarlimab adverse event rates are taken from GARNET. For the comparator arm the rates of adverse events for the individual treatments are taken from papers in the literature. These are then combined into a weighted average for RWEQ. Each adverse event is typically associated with a relevant inpatient NHS reference cost while the QALY impacts are typically taken from a range of previous NICE assessments.

Table 31: Adverse events: Costs and QALYs

	DOST	RWEQ	Cost	QALY
Abdominal pain	[redacted]		£375.46	-0.069
Allergic reactions		3%	£404.26	-0.116
Fatigue		4%	£0.00	-0.073
Anaemia	[redacted]	4%	£485.28	-0.119
Neutropenia		25%	£431.19	-0.090

Thrombocytopenia		5%	£655.62	-0.090
Nausea		1%	£447.58	-0.045
Vomiting		1%	£447.58	-0.103
Leukopenia		1%	£431.19	-0.090
Sensory neuropathy		2%	£351.03	-0.116
Hand and foot syndrome		3%	£404.26	-0.116
Mucosal inflammation		1%	£391.93	-0.151
Stomatitis		1%	£391.93	-0.151
Dostarlimab total			[redacted]	-0.021
RWEQ total			£214.93	-0.049

4.2.10 Other comparators

Given the extent of the submission and the focus on the company base case, the ERG has had only limited time to review the company modelling for the comparisons with the individual treatments. For each comparator it appears that this applies:

- The relevant OS hazard ratio to the unadjusted dostarlimab OS curve.
- The relevant PFS hazard ratio to the unadjusted dostarlimab PFS curve.
- The relevant PFS hazard ratio to the unadjusted dostarlimab TTD curve, but caps treatment at a maximum of 6 model cycles.
- The relevant direct drug costs and administration cost.

The company also performs similar scenario analyses using the company hazard ratios that it derives the RWEQ compared to dostarlimab.

4.3 *ERG critique of the company economics*

4.3.1 Model validation

The ERG has rebuilt the company model using the company assumptions and gets good agreement with the company model.

Table 32: Company model vs ERG model rebuild

	Company model			ERG model rebuild		
	RWEQ	DOST	net	RWEQ	DOST	net
QALYs	[redacted]					
Costs	[redacted]					
ICER			£37,311			£37,075

The ERG rebuild has identified one major error and a number of more minor errors in the company model structure.

- The major error is the calculation of treatment waning and the equalizing of dostarlimab effectiveness with the comparator RWEQ effectiveness as reviewed in greater detail in section 4.3.1.1 below. Correcting this error worsens the company base case ICER from £37,311 per QALY to £46,314 per QALY.

- There is an error in the calculation of the dostarlimab [redacted] cessation percentage. Correcting this error worsens the company base case ICER from £37,311 per QALY to £38,126 per QALY.

- The model assumes 3 weekly dosing of dostarlimab when from the 5th administration it is 6 weekly. Correcting this error worsens the company base case ICER from £37,311 per QALY to £38,098 per QALY.

- The company model assumes that dostarlimab patients who receive a subsequent treatment receive only 1 subsequent treatment while the GARNET trial data suggests more than 1 subsequent treatment. Correcting this error worsens the company base case ICER from £37,311 per QALY to £37,821 per QALY.

- For the scenario that includes a screening cost there is an error in the number needed to screen. This does not affect the company base case.

- While not a modelling error the company excludes doxorubicin + cisplatin from the RWEQ costing on the basis of it comprising less than 5% of those treated, but at [redacted] ([redacted]) this is peculiar and the ERG thinks it an error of judgement, in particular because it means that the company has not presented the effectiveness estimates for doxorubicin + ciplatin. But including doxorubicin + cisplatin has minimal effect upon the company base case, worsening the company base case ICER from £37,311 per QALY to £37,411 per QALY.

- While not a modelling error, at clarification the company noted that the submission quality of life values had been based on an [redacted] subset of the GARNET trial and not the [redacted] subset of the GARNET trial. Correcting this has little effect, worsening the company base case ICER from £37,311 per QALY to £37,428 per QALY.

The corrections worsen the company base case ICER from £37,428 per QALY to £49,190 per QALY. Sections 5.1 and 5.2, from page 146, reports the detail of the results for the company submission base case of £37,311 per QALY. But the intervening sections work with the £49,190 per QALY ICER, which the ERG will refer to as the ERG corrected company base case. The ERG thinks that the ERG corrected company base case is the more relevant figure to work with.

4.3.1.1 Treatment waning and equalisation of hazards with RWEQ

The company submission states that "*Treatment waning was assumed to end at* [redacted] *years, at which point, the efficacy associated with dostarlimab was assumed to be equal to the efficacy associated with current clinical management*". The company model applies the MAIC adjusted RWEQ hazard ratios to the dostarlimab curve hazards. It does not apply the RWEQ hazards from [redacted]. The OS hazards of the company base case are shown below.

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The MAIC OS HR of [redacted] is not applied in full at the start of [redacted]. Rather it is increased linearly from 0.000 at the start of [redacted] to 2.857 at the end of [redacted], and thereafter remains at [redacted]. The effect of this is seen in the upward tick in the OS hazard for dostarlimab during [redacted]. But the OS hazard for dostarlimab remains below that of RWEQ. The company model does not equalize the hazards between the arms from [redacted] onwards. Hazards are only equalized between the arms from around 20 years due to general population mortality rising above the company modelled hazards. The company base case assumes that a treatment effect from dostarlimab will be retained for around [redacted] after the vast majority have ceased treatment and [redacted] after all have ceased treatment.

There is much better correspondence between the two arms during the waning of PFS when the HR of [redacted] is applied. The odd behaviour of the hazards towards the end of the time horizon is due to the PFS ≤ OS constraint, hence the OS hazards being applied. Very few patients remain alive at this point.

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Given the company intention to equalize hazards between the arms from year [redacted] onwards, when equalizing hazards the ERG will equalize the dostarlimab hazard with the RWEQ hazard. During any period of waning, within the dostarlimab arm the ERG will take a weighted average of the dostarlimab hazard and the RWEQ hazard. If the number of cycles during the adjustment period is N the weight for the RWEQ hazard for the n^{th} cycle of this adjustment period will be n/N.

4.3.1.2 GARNET subsequent treatments

When costing subsequent treatments the company notes that [redacted] of those who ceased dostarlimab received a subsequent treatment. Among these [redacted] patients the average number of subsequent treatments, including [redacted] radiotherapy treatment and [redacted] letrozole treatments, was [redacted]. The company assumes that [redacted] will receive radiotherapy, [redacted] hormone therapy and the remainder the balance of the RWEQ 2L chemotherapies. But this yields an average number of subsequent treatments of [redacted] rather than the [redacted] of GARNET.

For the RWEQ data the proportion receiving a subsequent chemotherapy was [redacted]. It appears that radiotherapy and hormone therapy subsequent treatment data was not available. The company adds 10% radiotherapy and 5% hormone therapy to suggest a retreatment rate of [redacted]. This may be reasonable if the radiotherapy and hormone therapy data was not available within the RWEQ data.

The ERG thinks that it is more reasonable to apply the average number of subsequent treatments for dostarlimab, because this is what generated the clinical effectiveness estimates.

Note that subsequent treatment costs only include the direct drug costs. There are no drug administration costs. Including administration costs in the ERG model rebuild raises costs in both arms, but net costs and the ICER are barely affected by this omission. The ERG does not explore this further.

4.3.1.3 Quality of life values

The company submission notes that in GARNET only N=106 patients in the ITT population had EQ-5D data available due to EQ-5D only being collected following protocol amendment 3. The quality of life values are based upon the subset who have both a baseline and at least 1 post baseline value. The ERG assumes this is the reason for the reduction in the sample size from N=106 to N=[redacted]. The mean baseline quality of life value relates to the N=[redacted] and not the N=[redacted]. The ERG thinks that the company should supply the mean quality of life value for the N=[redacted] as well, as there may be an issue around which is the most appropriate to use for the calculation of the quality of life values within the model. This issue can be resolved at technical engagement by a presentation of both values and their standard errors.

4.3.1.4 Number needed to test

The calculation of the number needed to test (NNT) for testing costs suggests that of the 42% of recurrent patients, all 42% need tested. Given the £210 test cost this results in an average testing cost of £88. But the calculation incorrectly applies the assumed 23% dMMR prevalence, in effect not applying it. Applying this results in an NNT of 186% and an average testing cost of £390. The ERG is also unclear why only the

recurrent need to be tested. If all patients need to be tested the NNT rises to 443% and the average testing cost to £929.

The £210 cost per test is taken from NICE DG42, IHC screening for Lynch syndrome in people with endometrial cancer. Note that DG42 also includes a genetic counselling cost of £563. If this is included and all need to be tested, costs in the dostarlimab arm would increase by £1,268.

But ERG expert opinion notes that if NICE guidance is followed testing will be routine in all centres within the next 12-18 months. The ERG thinks that despite the NICE scope the company is correct not to include the costs of the tests.

4.3.2 Correspondence between model inputs and cited sources

4.3.2.1 TA571 treatment discontinuations

The company states that similar discontinuation assumptions were made during the STA of Avelumab for treating metastatic Merkel cell carcinoma (TA517). This is a slightly partial account.

- The company submission for TA517 assumed that 1/3 of patients projected to remain on treatment at 2 years by the log-logistic curve would continue treatment beyond it. All patients would stop treatment at 5 years.
- The ERG preferred to apply the Weibull with no treatment cessation rules as it seemed unethical to cease treatment for those continuing to benefit from it.
- The NHS England submission noted that "*several other PD-L1 drugs have 2 year maximum treatment durations in use, particularly in lung cancer. In those diseases in which PD-L1 drugs have been used for the longest, there is an increasing perception amongst clinicians that very long treatment durations may not be necessary and may cause harm in view of the uncommon but potentially very serious immune-related toxicities that are being encountered with prolonged treatment durations.*"
- The FAD concluded that "*The committee agreed that the company's assumptions appeared to reflect clinical practice with regard to stopping treatment. However, it*

concluded that it would consider both the company's and the ERG's assumptions in its decision-making."

4.3.3 ERG critique: Main Issues

4.3.3.1 Uncertainty around long term clinical effect

The limited duration of follow-up during GARNET and the structural uncertainties around treatment cessation and duration of benefit mean there is considerable uncertainty about the reliability of the long-term modelling. This is reflected in the ERG corrected company base case ICER sensitivity to the time horizon that is applied. Quite a long extrapolation is required for the ICER to approach the NICE upper End of Life willingness to pay (WTP) threshold of £50k/QALY.

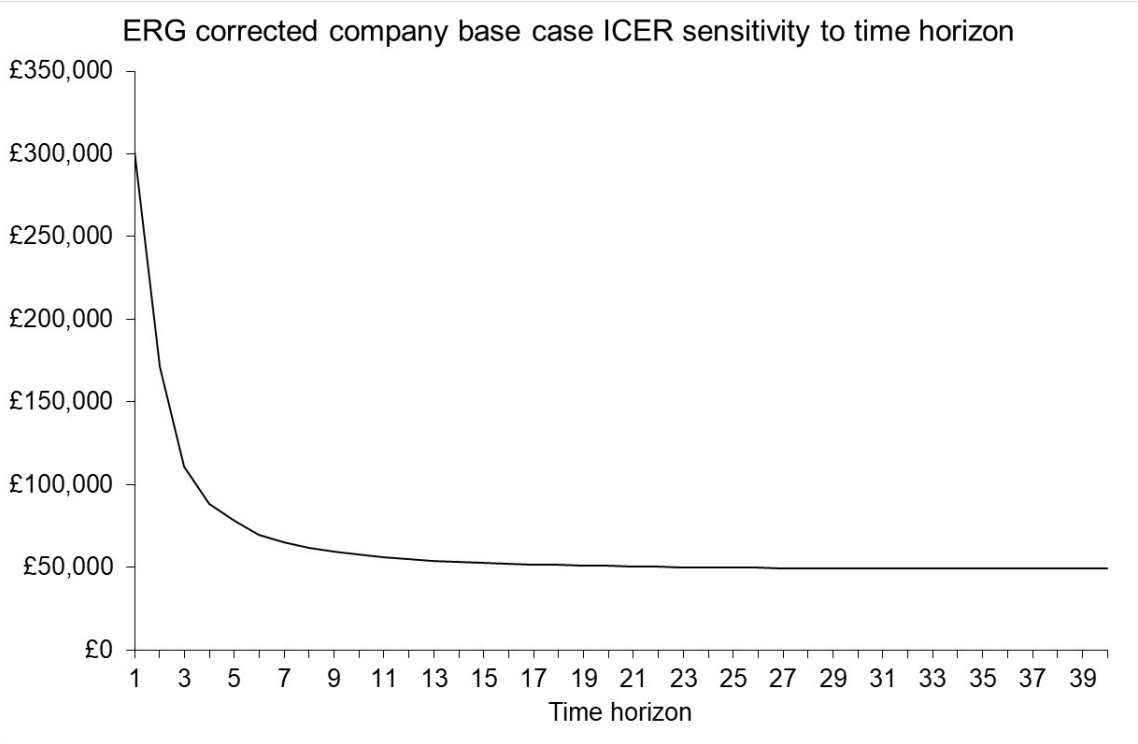


Figure 25: ERG corrected company base case: ICER sensitivity to time horizon

4.3.3.2 OS and PFS extrapolation: Elicitation

The company's seven experts were shown the GARNET Kaplan Meier S(t) curves and the 6 monthly numbers remaining at risk for the ITT and the evaluable efficacy populations, and the equivalent of this for the RWEQ data set. They were asked to complete the following table.

Table 33: Company expert elicitation: OS projections

	6mth	12mth	18mth	24mth	3yr	5yr	10yr	15yr	20yr
DOST									
RWEQ									

The experts were then shown the GARNET Kaplan Meier OS S(t) curve with the unadjusted OS parameterised curves fitted to it and extrapolated to 20 years. They were asked to state which of the unadjusted parameterised OS curves best represented the proportion who would remain alive. A similar exercise was then performed for the RWEQ Kaplan Meier OS S(t) curve and OS parameterised curves.

A parallel exercise was then undertaken for PFS, with the experts being asked to complete the following table and then decide on which of the unadjusted parameterised curves was the most reasonable extrapolation.

Table 34: Company expert elicitation: PFS projections

	6mth	12mth	18mth	24mth	3yr	5yr	10yr	15yr	20yr
DOST									
RWEQ									

The key point is that the experts were never asked about the parameterised curves adjusted for dostarlimab treatment stopping rules. The OS and PFS elicitation exercises were conducted prior to the discussions around treatment stopping rules and treatment waning. It can be argued that the experts might have this in the back of their mind in any case, but the presentation of the unadjusted curves during the elicitation exercise suggests the opposite was anticipated by the company.

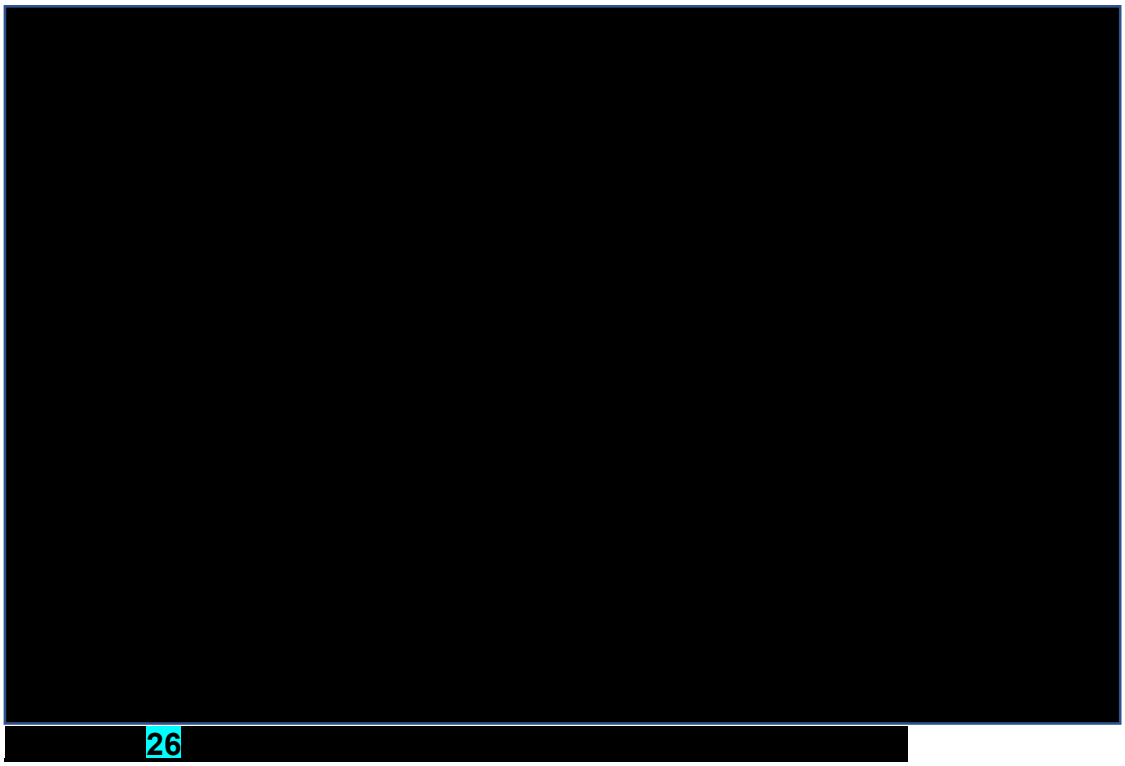
The ERG thinks that the most reasonable interpretation of the company expert estimates for OS and PFS relate to the GARNET data and to the unadjusted curves.

The ERG thinks that it is unreasonable for the company to have presented these results within its submission results overlaid on the dostarlimab adjusted curves. The ERG thinks that the company expert responses will be biased and too high for an assessment of the reasonableness of the adjusted curves.

Given the issues highlighted above, the ERG undertook further in-depth critique of the company's approaches to modelling OS and PFS extrapolation, and selected Weibull as the preferred parametric model for OS (see Appendices 9.3 and 9.4).

4.3.3.3 Treatment discontinuation and waning: Elicitation

Subsequent to the OS and PFS elicitation, the company experts were shown a graph similar to Xxxxxxx26 below. The ERG has superimposed the TTD Kaplan Meier S(t) curve and the Kaplan Meier % N at risk curve out to two years, though note that as presented in Xxxxxxx8 on page 101 above the GARNET TTD KM data extends beyond this. The ERG Kaplan Meier % N at risk are typically higher than those of the company. It is difficult to know quite what data points the company presentation relates to as some span periods up to 6 weeks, but even given this the ERG cannot align its N at risk with that of the company presentation. This could be due to ERG error, company error or the company presentation may be using an earlier data cut which would result in earlier censoring due to data cut off and hence lower numbers remaining at risk than applies in the IA2 data cut used by the ERG. The reason for the increase from [redacted] for 31w-36wpatients to [redacted] patients for 37w-42w in the company presentation is apparently due to the inclusion of a patient who received a delayed dose.



The experts were also shown the following tabulated values.

Table 35: Company TTD elicitation table

	0mth	3mth	6mth	9mth	12mth	>12mth	2yr
%							
N							

In effect, the experts were shown the blue bars of Xxxxxxx26 with labels showing the proportion and number of patients remaining on treatment, and the values of Table 35.

Note that the experts were not asked to complete the final table entry as in the OS and PFS elicitation exercises, but were rather presented with it prefilled at [redacted] The ERG thinks that it would have been better to have asked the experts to complete this themselves much as with the OS and PFS elicitation.

The key point is that the company seems to have presented the number remaining at risk and not the Kaplan Meier TTD S(t) curve. If so the company presentation assumes

that censoring due to data cut off is a discontinuation event. This would be incorrect and would seriously bias the presentation.

It is also notable that the company only presents the KM numbers remaining at risk to "[redacted]" weeks and "[redacted]" with the value for this "timepoint" being [redacted]. The [redacted] remaining at risk applies to weeks [redacted], somewhat closer to week 54 than the uninformed observer might be expected given the company presentation. But noting this might have resulted in an infeasibly low proportion being estimated to remain on treatment at the [redacted] point, a reflection of the number at risk falling off due to data cut off despite the Kaplan Meier S(t) curve being maintained.

The Kaplan Meier TTD data extends some time beyond this but the longer presentation would have shown a further decline in the KM numbers at risk due to the data cut-off, as per the ERG superimposed curves of Xxxxxxx26.

The ERG thinks that to elicit the desired result the company has presented an invalid data set that appears to show a smooth steady fall in the number of patients remaining on dostarlimab, and hence the reasonableness of assuming that this smooth steady discontinuation rate will broadly continue to yield around [redacted]. The experts are not presented with the resulting modelled curve which applies the [redacted] assumptions to the curve fitted to the Kaplan Meier S(t) data, resulting in the cliff edge discontinuation at [redacted]. The modelled TTD curve bears no resemblance to the numbers remaining on treatment that were presented to the experts.

The ERG thinks that the company should have presented the Kaplan Meier S(t) curve estimates for TTD. The ERG thinks that presenting the Kaplan Meier number remaining at risk and so in effect treating data cut off as a discontinuation event renders the company TTD elicitation exercise largely meaningless. At best it would seem to put a lower floor on what proportion might remain on treatment but the values cannot be used as central estimates.

Of the questions:

- [redacted] As this was a Yes/No question it appears there was no way for the experts to dissent by suggesting a different percentage.
- [redacted] As this was a Yes/No question it appears there was no way for the experts to dissent by suggesting another timepoint. The ERG also notes that there is no stopping rule in the SmPC. It is unclear whether the company is suggesting that if NICE approves dostarlimab that a stopping rule at [redacted] should be a part of the recommendation and funding. ERG expert opinion suggests that there will only be a cliff edge if funding is withdrawn at this point.
- [redacted] This presumes that a stopping rule at [redacted] will be introduced. The restriction of the responses to be no more than [redacted] is also a concern, particularly in the light of two respondents choosing this value and possibly being constrained by it causing the [redacted] to be biased and too low.

The presentation also suggests that the experts were asked:

[redacted]The ERG has not been able to find any responses to these questions. The second question is slightly loosely worded in that it does not specify that this should be among those who have discontinued treatment. It also has surprisingly

long durations as options, with there being no means for the experts to be any more explicit about short durations such as “[redacted]” other than by stating “[redacted]”.

The company did not ask the seven experts about complete cessation of dostarlimab. It appears that this was only asked of two of the seven experts during follow-up one-to one interviews. It is unclear whether either of these experts were either of the two of seven experts who tended to disagree with the pre-specified responses of the main elicitation exercise. The two experts who were consulted apparently noted that [redacted]The SmPC states “Treatment can be continued as long as Jemperli continues to work. The doctor may interrupt Jemperli treatment or stop it altogether if certain side effects occur”. This appears to put the emphasis on reacting to the occurrence of side effect, rather than pre-emptively withdrawing treatment.

ERG expert opinion thinks that the cliff edge discontinuation of the company base case is only likely to apply if funding is withdrawn after [redacted] of treatment. Both experts note the possibility of a range of adverse events. Patients remaining progression free and doing well while receiving dostarlimab may not want to have it withdrawn from them. One ERG expert notes that patients find repeated ongoing treatment a burden which could be a contributory factor to treatment cessation in addition to the side effects mentioned in the SmPC.

There is some disagreement between the ERG experts as to when patients remaining progression free while on dostarlimab might start to have treatment withdrawn. One suggests that toxicity could see some withdrawing from treatment as early as [redacted], though the ERG thinks that withdrawals while progression free that are related to toxicity might already be reflected in the GARNET TTD data. This expert suggests that most patients would have withdrawn from treatment at [redacted] but that some would continue beyond this point, while the other expert suggests that rather more patients

remaining progression free could continue dostarlimab treatment beyond [redacted]. Similarly, one ERG expert thinks a [redacted] total cessation point is reasonable, while the other queries why patients who are progression free would cease treatment even at the [redacted] point.

The ERG questions why the TTD and stopping rules elicitation exercise was conducted after the OS and PFS elicitation exercise. Unbiased OS and PFS estimates adjusted for the TTD and treatment stopping rules obviously require prior consideration of the TTD and stopping rules.

The ERG thinks that the company TTD and stopping rules elicitation exercise was poorly constructed, that its results are likely to be biased and that at best it provides a floor to the cessation percentage. Given this the ERG will apply a percentage of [redacted] and will explore [redacted] and [redacted]. In the light of the SmPC the ERG will constrain the proportion on treatment after the first cessation point to be the lesser of the TTD curve and the PFS curve.

The company does not appear to have presented data to support its assumption that those ceasing dostarlimab would continue to receive the full benefits of treatment for [redacted] after stopping treatment. There may be retention of benefits but the ERG thinks it unlikely that no patient would have any loss of effect for [redacted] after treatment cessation.

The ERG thinks that the more natural assumption is that for some patients some loss of effect, albeit small, would start from treatment cessation. As a consequence, the ERG base case will assume that treatment waning occurs from the point of treatment cessation. This does not assume that patients revert to the RWEQ risks immediately upon treatment cessation, only that they move towards these risks from treatment cessation. A treatment benefit is still assumed for [redacted] after treatment cessation, which in itself may be optimistic.

4.3.3.4 Treatment discontinuation and waning: Scenarios

Given the questionable reliability of the company TTD elicitation exercise the ERG presents various scenarios to illustrate the effect that altering these assumptions has upon the ERG corrected company base case. For all scenario all dostarlimab patients are assumed to cease treatment at the start of year 5

Table 36: Corrected Company ICER: Sensitivity to discontinuation assumptions

First discontinuation rules		Waning of effect period		
Year	% remaining	Start Year	End Year	ICER
[redacted]	[redacted]	[redacted]	[redacted]	£49,190
[redacted]	[redacted]	[redacted]	[redacted]	£55,354
[redacted]	[redacted]	[redacted]	[redacted]	£51,900
[redacted]	[redacted]	[redacted]	[redacted]	£47,223
[redacted]	[redacted]	[redacted]	[redacted]	£53,590
[redacted]	[redacted]	[redacted]	[redacted]	£60,362
[redacted]	[redacted]	[redacted]	[redacted]	£56,568
[redacted]	[redacted]	[redacted]	[redacted]	£51,429
[redacted]	[redacted]	[redacted]	[redacted]	£57,990
[redacted]	[redacted]	[redacted]	[redacted]	£65,369
[redacted]	[redacted]	[redacted]	[redacted]	£61,235
[redacted]	[redacted]	[redacted]	[redacted]	£55,635
[redacted]	[redacted]	[redacted]	[redacted]	£56,315
[redacted]	[redacted]	[redacted]	[redacted]	£54,034
[redacted]	[redacted]	[redacted]	[redacted]	£51,894
[redacted]	[redacted]	[redacted]	[redacted]	£59,563
[redacted]	[redacted]	[redacted]	[redacted]	£57,139
[redacted]	[redacted]	[redacted]	[redacted]	£54,864
[redacted]	[redacted]	[redacted]		

Assuming that waning starts immediately upon treatment cessation or [redacted] after treatment cessation worsens the ICER by a reasonable amount. Note that these scenarios still retain a waning dostarlimab treatment effect out to [redacted], [redacted] after treatment has ceased for most patients.

Results are particularly sensitive to moving the timepoint of the first main discontinuation from [redacted] years to [redacted] years,

There needs to be detailed consideration of the cliff edge that is assumed for discontinuations.

4.3.3.5 Censoring by arm and informative censoring

The OS KM S(t) and N at risk as a proportion of baseline N can be presented for GARNET ITT and the RWEQ population.

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There is much higher censoring in the GARNET data than the RWEQ data. If the above pattern of censoring was observed in a two arm trial it would raise major concerns. There is also a large amount of early censoring in the GARNET data, which is a concern.

It is possible that those who performed badly during GARNET were more likely to drop out of the trial and be censored while those with a better performance were more likely to continue with treatment and remain in the trial.

At clarification the ERG asked for GARNET KM data restricted to those with a CR or PR response. The company declined to supply this on the grounds that as this would only apply to [redacted] patients the reduced sample size means that it would not be appropriate to draw any conclusions from this data.

Fully exploring this would need to take into account censoring due to data cut off and censoring due to other reasons. The ERG clarification KM data request for the ITT, evaluable efficacy and those with a CR or PR response populations would need to be augmented by splitting the censoring column into censoring due to data cut off and censoring due to other reasons. Patient baseline characteristics split by best response and reason for censoring, data cut or other, would also be required. This is an issue that can be addressed at technical engagement.

4.3.3.6 RWEQ individual treatment effects

The pooled RWEQ GARNET like OS KM curve can be compared with the RWEQ 5 most common treatments' individual KM curves. Note that the company declined to supply the KM curve for cisplatin + doxorubicin mainly due to it falling marginally below the arbitrary 5% of RWEQ patients threshold that the company uses for costing purposes ([redacted]) and not being within the NICE scope. With regards the latter is can be noted that the cisplatin + doxorubicin clinical effectiveness remains within the RWEQ data, that the NICE scope specifies chemotherapy "including" a number of named treatments and that the NICE scope also does not specifically name carboplatin+PLD. Treatments comprising more than 5% of the RWEQ GARNET like ([redacted]) data set accounted for [redacted] of patients.

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Xxxxxxx28 shows the marked differences in overall survival by treatment within the RWEQ data set. The combination therapies had better survival and the monotherapies worse survival.

Table 37: RWEQ baseline characteristics by treatment

	Carb+Pac	Carb+PLD	PLD mono	Pac mono	Carb mono
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age					
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
< 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
65 - 75 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG at registry diagnosis					
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Known	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
of which 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
of which 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology at diagnosis					
Clear cell carc.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endometrioid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed carc.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-spec. carc.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIGO at registry diagnosis					
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade at diagnosis					
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

There are few marked differences in the patient baseline characteristics presented by the company that could account for these large differences, though the following might be noted:

- Fewer younger patients for PLD monotherapy and carboplatin monotherapy

- Higher unknown ECOG for PLD monotherapy and carboplatin monotherapy

The lower proportion of younger patients under 65 for PLD monotherapy and carboplatin monotherapy mirrors the lower proportion of younger patients in the RWEQ population, [redacted], compared to the GARNET population [redacted]. The GARNET forest plot of Figure 20 (Document B, page 74) showed no difference in ORR between those under 65 and those over 65, but this does not necessarily imply that there was no difference in overall survival.

The high proportion with unknown ECOG status may be of concern, given that GARNET found it to be a statistically significant determinant of the likelihood of response.

ERG expert opinion is that there are likely to be possibly quite large imbalances between the GARNET and RWEQ populations, and that the best means of exploring this might be to consider the endometrioid subgroups of GARNET and RWEQ populations.

At clarification the ERG requested GARNET and RWEQ KM data split by ECOG status and by endometrioid status. The company declined to supply this, though noted that it was exploring the possibility of supplying data according to endometrioid status. This can be resolved during technical engagement.

4.3.3.7 Dostarlimab PFS vs TTD

As outlined in section 4.2.6.7, the company base case PFS and TTD parameterized curves almost coincide for the first two years of the model, the areas under the curves (AUC) being [redacted] months and [redacted] months respectively: a ratio of 1.04.

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During GARNET a reasonably higher proportion of patients remained on treatment compared to remaining in PFS between months 2 and 8. The ERG will present a scenario that applies the GARNET TTD KM curve for the first 8 months of the model.

4.3.3.8 Choice of TTD curve

The company choice of the log-logistic TTD curve does not appear to be justified on statistical grounds. As outlined in greater detail in section 4.2.6.1 on page 101, the Gompertz TTD curve has lower information criteria. Since the dostarlimab TTD curve is mainly being applied prior to the first cessation point and so during the period for which Kaplan Meier data is available, there is less need to assess the reasonableness of extrapolation. The information criteria can be used to assess the internal goodness of fit.

Following detailed critique of the company's approaches and alternative options (see ERG report Appendix 9.5), the ERG prefers the company Gompertz over the company log-logistic dostarlimab TTD curve. This worsens the ERG corrected company base

case from £49,190 per QALY to £51,804 per QALY. But for its base case the ERG prefers the ERG ITT generalized gamma which worsens the ERG corrected company base case from £49,190 per QALY to £52,548 per QALY.

4.3.4 ERG critique: Other issues

4.3.4.1 Quality of life model

The company supplies a range of additional quality of life regressions that explore varying the number of 3 week cycles from death. The quality of life values for the various health states are the exponential of the sum of the relevant coefficients, the baseline QoL coefficient being qualified by the GARNET baseline quality of life of [redacted].

Cycles to death	0	1	2	3	4
Constant Baseline QoL Progressed Cycles to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycles to death	5	6	7	8	9
Constant Baseline QoL Progressed Cycles to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
**significant at 1%, *significant at 5%					

In general, the inclusion of a time to death variable makes the coefficient for progressed disease not statistically significant. The exception to this is the model that examines 4 cycles from death. But it seems likely that there is a high degree of multicollinearity between the two variables. The QIC criteria also do not obviously favour the choice of 5 cycles.

Given the centrality of the PFS and PPS health states to the model the ERG thinks it is peculiar to introduce the time to death variable if this renders the PPS coefficient not statistically significant. The QIC criteria also tend to favour either not including time to

death, or including a lengthy time to death which in effect makes consideration of progression redundant. The company is also concerned about the number of observations retained in each analysis, the ERG noting that the analysis with no time to death variable has largest number of observations. But the differences in the main quality of life values are not large.

[redacted]30[redacted]

The ERG also notes that the application of the PFS EoL QoL value and the PD EoL QoL value requires that deaths occurring in the next 5 cycles be modelled as occurring either from PFS or from PD. The model assumption is that these deaths will be proportionate to the number of patients in PFS compared to the number of patients in PD which may not be realistic. The ERG thinks that this is a further argument against including the time to death variable.

The ERG thinks that the natural approach for the base case is not to include the time to death variable. This revision has minimal effect, only slightly worsening the ERG corrected company base case from £49,190 per QALY to £49,513 per QALY.

4.3.4.2 Quality of life values in the literature

The NICE scope does not list any relevant previous STAs. The company SLR identifies 3 studies from the literature, dismissing them due to either small sample size or being based upon expert opinion. The ERG broadly agrees with this but notes that the German study (n=20) reports EQ-5D values of 0.701 for primary disease (N=9) and 0.676 for advanced disease (N=11), though these are valued using a German TTO tariff. These are broadly similar to the company model with no time to death variable estimates of [redacted] for PFS and [redacted] for PD.

4.3.4.3 RWEQ mean number of model treatment cycles

Within its costings of RWEQ as subsequent treatment to dostarlimab the company uses the RWEQ 2nd line data of the RWEQ arm. The company also notes that the median number of model cycles that patients remained on treatment within this was [redacted]. The company base case simulates a mean number of model cycles of [redacted]. This may suggest reducing the modelled RWEQ drug and administration costs to [redacted] cycles; i.e. multiplying by a factor of 84%. This worsens the ERG corrected company base case ICER from £49,190 per QALY to £49,443 per QALY.

4.3.4.4 RWEQ costing

The RWEQ costing calculates an average cost per model cycle based upon the baseline balance of treatments, then applies this to the pooled RWEQ TTD curve. The individual treatment TTD KM curves vary wildly, much as per the individual treatment OS KM curves. It is not obvious whether this is likely to result in much bias, but it can be noted that PLD is one of the more expensive treatments but has very poor KM curves.

4.3.4.5 RWEQ PLD costing

The PLD cost is based upon an average BSA of [redacted] resulting in a dose of [redacted]. This is marginally above the 70mg dose that could be supplied with a 20mg and a 50mg vial at a drug cost of £1,073 rather than £1,425. It might have been more reasonable to

assume a 50:50 split between dosing under and dosing over 70mg, which would slightly lessen the direct drug cost per 4 week treatment cycle from £1,425 to £1,248.

RWE data apparent suggests a [redacted] balance between doxorubicin and PLD, but model costing assumes all PLD. Doxorubicin is somewhat cheaper than PLD.

The above considerations would worsen the ICER. Time constraints mean that the ERG has not explored this. The ERG thinks that the effect would be relatively minor.

4.3.4.6 Ongoing costs

The PFS on treatment, PFS off treatment and PPS health states incur reasonable costs due to ongoing monitoring.

ERG expert opinion suggests that the company estimates for PFS on treatment may be too resource intensive. Given the hospital based monitoring GP and community nurse visits may be less likely.

ERG expert opinion suggests that the company estimates for PFS off treatment may be too resource intensive. Consultant OP visits might be only every 12 weeks. And OP specialist nurse visits might also be less frequent. CT scans might initially be 3 monthly but this would probably extend to 6 months.

In the light of this the ERG will for:

- PFS on treatment, exclude GP and community nurse visits
- PFS off treatment, extend consultant OP visits to 12 weeks and CT scans to 6 monthly

This improves the ERG corrected company base case ICER from £49,190 per QALY to £48,735 per QALY.

The ERG will also present a scenario the extends the PFS off treatment OP specialist nurse visit frequency to 12 weekly.

4.3.4.7 GARNET trial population and test sensitivity and specificity

The company reports that the test is also associated with a sensitivity of 96.2% and a specificity of 88.4%. If these values carry across to the current setting the relatively low specificity may be a concern. Given the assumed prevalence of 23%, it suggests that

among those with a positive test 71% would be true positives and 29% would be false positives. Almost a third of those testing positive and so being treated with dostarlimab may not be dMMR. How this tallies with the GARNET population and what impact this might have upon the real world effectiveness of dostarlimab compared to that in GARNET is difficult for the ERG to speculate about.

5 COST EFFECTIVENESS RESULTS

5.1 *Company's cost effectiveness results*

The original company submission included a dostarlimab PAS of [redacted], and a base case ICER of £50,221 per QALY. During technical engagement the company has increased its PAS to [redacted]. The results of this section revise the company estimates of its original submission by applying the [redacted] PAS rather than the original [redacted] PAS.

The undiscounted life years and discounted QALYs are presented in Table 38.

Table 38: Company base case: Survival and QALYs

	Undiscounted LY			Discounted QALYs		
	RWEQ	DOST	Net	RWEQ	DOST	Net
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The company base case anticipated that around two thirds of survival in the dostarlimab arm will occur after progression, with around three quarters of the net QALY gain also occurring after progression.

The disaggregate discounted costs are presented in Table 39.

Table 39: Company base case: Disaggregate costs

	RWEQ	DOST	Net
Diagnostic	[redacted]	[redacted]	[redacted]
Drug	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
PFS ongoing	[redacted]	[redacted]	[redacted]
Subsequent Treatment	[redacted]	[redacted]	[redacted]
PPS ongoing	[redacted]	[redacted]	[redacted]
End of Life	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

These results in the cost effectiveness estimate of Table 40.

Table 40: Company base case: Summary

	RWEQ	DOST	Net
LY	[redacted]	[redacted]	[redacted]
QALY	[redacted]	[redacted]	[redacted]
Cost	[redacted]	[redacted]	[redacted]
ICER			£37,311

As noted in the executive summary, at clarification the company supplied slightly revised quality of life values due to basing this on [redacted] rather than [redacted], which very slightly worsens its base case, together with a set of scenario analyses. Due to time constraints the ERG has not updated the company model results for this. This is unlikely to affect Committee deliberations. The ERG revised base case and scenario analyses do reflect the revised quality of life model.

The probabilistic model has a slightly better central estimate of £35,492 per QALY with the associated CEAC being presented in Xxxxxxx31.

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The probabilities of dostarlimab being cost effective at the various NICE willingness to pay thresholds are presented in Table 41.

Table 41: Company base case probabilities of cost effectiveness

	Standard		End of Life	
	Threshold	Probability	Threshold	Probability
Lower threshold Upper threshold	[redacted]	[redacted]	[redacted]	[redacted]
* Applying the NICE methods 1.7 QALY multiplier				

5.2 *Company's sensitivity analyses*

The company presents a range of univariate sensitivity analyses, the tornado diagram for the 10 most influential variables being presented in Figure 61 on page 197 of Document B of the company submission. The company base case is most sensitive to: baseline utility, the health state utilities and the cost per cycle of dostarlimab. Given the company base case ICER these are all prone to pushing the ICER further above and below £50k per QALY.

The company also presents an extensive range of scenario analyses in Table 85 on page 206 of Document B of the company submission. The ERG does not replicate these in full but highlights a subset of them in Table 42. Unfortunately, time constraints mean that the ERG has not been able to update these company scenario analyses for the revised [redacted] PAS. As a consequence, they relate to the original company PAS of [redacted] and associated base case of [redacted] per QALY.

Table 42: Selection of company scenario analyses

	Δ Cost	Δ QALY	ICER
Company base case (Previous PAS of [redacted])	[redacted]	[redacted]	£50,221
RWEQ based upon EGOG01 ([redacted])	[redacted]	[redacted]	£49,155
RWEQ based upon MAIC OS HR [redacted]	[redacted]	[redacted]	£54,249
RWEQ based upon MAIC OS HR [redacted]	[redacted]	[redacted]	£52,917
DOST OS log-normal, no waning	[redacted]	[redacted]	£50,997
DOST OS generalised gamma, no waning	[redacted]	[redacted]	£33,677
[redacted]	[redacted]	[redacted]	£55,804
[redacted]	[redacted]	[redacted]	£45,439
[redacted]	[redacted]	[redacted]	£53,633
Inclusion of screening test	[redacted]	[redacted]	£50,261
Individual treatment comparator: Doxorubicin monotherapy			
PFS HR [redacted] Makker, OS [redacted] HR Zoptec	[redacted]	[redacted]	£63,144
PFS HR [redacted] Makker, OS [redacted] HR McMeekin	[redacted]	[redacted]	£55,284
PFS HR [redacted] Makker, OS [redacted] HR Makker	[redacted]	[redacted]	£41,337
PFS HR [redacted] Makker, OS [redacted] HR Julius	[redacted]	[redacted]	£40,439
Individual treatment comparator: Paclitaxel monotherapy			
PFS HR [redacted] Makker, OS [redacted] HR McMeekin	[redacted]	[redacted]	£56,911
Individual treatment comparator: Carboplatin + paclitaxel			
PFS HR [redacted] and OS [redacted] Rubenstein	[redacted]	[redacted]	Dom'ted
PFS HR [redacted] and OS [redacted] Mazgani	[redacted]	[redacted]	£106k
Dom'ted: Carboplatin + paclitaxel dominates dostarlimab			

The ERG also highlights that the company restricts it exploration of the alternative functional forms of dostarlimab OS to the log logistic, log normal and generalised gamma.

The ERG has not had time to check whether the no waning scenarios also assume no treatment cessation with patients following the base case TTD curve. The ERG has not had time to check whether the treatment waning that applies to dostarlimab when the

individual comparators are being considered applies the hazards of the individual comparators or retains the hazards of the pooled RWEQ curves. This can be addressed during technical engagement.

5.3 *ERG corrected company base case*

For completeness the ERG presents the ERG corrected company base case results. The undiscounted life years and discounted QALYs are presented in Table 43.

Table 43: ERG corrected company base case: Survival and QALYs

	Undiscounted LY			Discounted QALYs		
	RWEQ	DOST	Net	RWEQ	DOST	Net
PFS	[redacted]					
PPS						
AEs						
Total						

The ERG corrected company base case still anticipates that around two thirds of survival in the dostarlimab arm will occur after progression, with around two thirds of the net QALY gain also occurring after progression.

The disaggregate discounted costs are presented in Table 44.

Table 44: ERG corrected company base case: Disaggregate costs

	RWEQ	DOST	Net
Diagnostic	[redacted]		
Drug			
AEs			
PFS ongoing			
Subsequent Treatment			
PPS ongoing			
End of Life			
Total			

These results in the cost effectiveness estimate of Table 45.

Table 45: ERG corrected company base case: Summary

	RWEQ	DOST	Net
LY	[redacted]		

QALY Cost	[redacted]	[redacted]	[redacted]
ICER			£49,190

The probabilistic model has a slightly better central estimate of £48,764 per QALY with the associated CEAC being presented in xXxxxxxx32.

[redacted]32[redacted]

The probabilities of dostarlimab being cost effective at the various NICE willingness to pay thresholds are presented in Table 46.

Table 46: ERG corrected company base case probabilities of cost effectiveness

[redacted]

	Standard		End of Life	
	Threshold	Probability	Threshold	Probability
Lower threshold Upper threshold	[redacted]	[redacted]	[redacted]	[redacted]
* Applying the NICE methods 1.7 QALY multiplier				

5.4 *Company base case: Technical engagement*

As noted in the ERG review of the company TE submission the model submitted by the company at TE was submitted late and did not obviously implement the revised company waning. As a consequence, the ERG cannot replicate the company TE base case. The company TE base case with the ERG waning method applied is stated as resulting in a similar ICER of £49,608 per QALY. This is very similar to the ERG corrected company base case of £49,190 per QALY of Table 45 above, though it should be borne in mind that the ERG corrected company base case applies the original dostarlimab ToT data and not the company TE updated dostarlimab ToT data.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 *Exploratory and sensitivity analyses undertaken by the ERG*

6.1.1 ERG preferred assumptions

The ERG prefers the Weibull for dostarlimab OS whereas the company prefers the generalised gamma. The choice of dostarlimab is a major driver of results. Due to the company error the company submission presentation of the OS curves adjusted for waning is also incorrect. The ERG presents these for the Weibull and the generalised gamma over the 40 year time horizon of the model, alongside the GARNET OS KM curve. The waning assumptions are the ERG preferred [redacted] at [redacted] with waning over the next [redacted], after which all cease dostarlimab. The ERG also tabulates the modelled OS percentages for the range of curves available.

The proportions of patients modelled as surviving are presented in Table 47.

Table 47: ERG adjusted dostarlimab modelled OS by curve

Year	GGAM	WEIB	GAMM	EXPO	LOGL	LOGN	GOMP	KM
0.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Given the centrality of the choice of dostarlimab OS curve, the ERG presents a full set of analyses for its preferred base case using the Weibull, and also for the scenario of using the company preferred generalised gamma.

Table 48: ERG preferred model assumptions

Preferred assumption	Section	ICER
Company base-case	5.1	£37,311
ERG corrected company base-case	4.3.1	£49,341
ERG01: Dostarlimab OS Weibull	4.2.6.5 4.3.3.2	£65,454
ERG02: Dostarlimab ERG ITT TTD GGAM	4.3.3.8	£52,709
ERG03: [redacted] dostarlimab continue	4.3.2.1 4.3.3.3	£49,341
ERG04: Waning from treatment cessation	4.3.2.1 4.3.3.3	£55,523
ERG05: Quality of life – no time to death coefficient	4.3.4.1	£49,513
ERG06: Ongoing resource use	4.3.4.6	£48,885
Cumulative effect: ERG02-ERG06	..	£64,006
Cumulative effect: ERG01-ERG06	..	£79,714

6.1.2 ERG preferred base case

The undiscounted life years and discounted QALYs are presented in Table 49.

Table 49: ERG base case: Survival and QALYs

	Undiscounted LY			Discounted QALYs		
	RWEQ	DOST	Net	RWEQ	DOST	Net
PFS	[redacted]					
PPS						
AEs						
Total						

The ERG base case anticipates that survival in the dostarlimab arm is split more equally between PFS and PPS, though the majority of the QALY gain is still modelled as occurring after progression has occurred. This arises because the modelled OS curve lies some what above the modelled PFS curve.

The disaggregate discounted costs are presented in Table 50.

Table 50: ERG base case: Disaggregate costs

	RWEQ	DOST	Net
Diagnostic	£0	£0	£0
Drug + admin	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
PFS ongoing	[redacted]	[redacted]	[redacted]
Subsequent Treatment	[redacted]	[redacted]	[redacted]
PPS ongoing	[redacted]	[redacted]	[redacted]
End of Life	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

These results in the cost effectiveness estimate of Table 51.

Table 51: ERG base case: Summary

	RWEQ	DOST	Net
LY	[redacted]	[redacted]	[redacted]
QALY	[redacted]	[redacted]	[redacted]
Cost	[redacted]	[redacted]	[redacted]
ICER			£79,714

The probabilistic model has an ICER of £80,640 per QALY with the associated CEAC being presented in Xxxxxxx34.

34

The probabilities of dostarlimab being cost effective at the various NICE willingness to pay thresholds is presented in Table 52.

Table 52: ERG base case probabilities of cost effectiveness

	Standard		End of Life	
	Threshold	Probability	Threshold	Probability
Lower threshold Upper threshold	[redacted]	[redacted]	[redacted]	[redacted]
* Applying the NICE methods 1.7 QALY multiplier				

As already noted the Weibull OS curve has a major impact upon results. If the company preferred generalised gamma is applied the deterministic ICER is £64,006 per QALY. The probabilistic ICER is £63,366 per QALY, the CEAC being presented in Xxxxxxx35.

35

If the company OS generalised gamma is retained the probabilities of dostarlimab being cost effective at the various NICE willingness to pay thresholds is presented in Table 53.

Table 53: ERG base case probabilities of cost effectiveness but retaining company OS generalised gamma.

	Standard		End of Life	
	Threshold	Probability	Threshold	Probability
Lower threshold Upper threshold				
* Applying the NICE methods 1.7 QALY multiplier				

6.1.3 ERG scenario analyses

The ERG presents the following scenario analyses:

- SA01: Assuming dostarlimab treatment cessation from [redacted] and from [redacted], retaining the assumption that all cease treatment at [redacted].

- SA02: Assuming proportions remaining on dostarlimab at [redacted] of [redacted] and [redacted].
- SA03: Assuming treatment waning starts [redacted] and [redacted] after the treatment cessation at [redacted].
- SA04 Applying the company Gompertz and company log-logistic dostarlimab TTD curves, based upon the original TTD KM data of the original company submission, and the log-normal dostarlimab TTD curve based upon the updated TTD KM data, as used within the company TE submission. Note that the ERG base case generalised gamma TTD curve has always been based upon the updated TTD KM data.
- SA05: Applying the dostarlimab TTD KM curve for the first 8 months of the model.
- SA06: Applying the quality of life values of the German study: PFS 0.701 and PPS 0.676.
- SA07: Applying a correction factor to the RWEQ treatment costs to align the modelled treatment duration with the mean stated by the company.
- SA08: Reducing the frequency of visits to the specialist nurse when in PFS off treatment to 12 weekly.
- SA09: Time horizons of 10, 20 and 30 years.
- SA10: Applying the upper and lower confidence intervals of the dostarlimab OS curve
- SA11: Applying the upper and lower confidence intervals of the dostarlimab OS, PFS and TTD curve

The deterministic cost effectiveness estimates for these scenarios are presented in Table 54.

Table 54: Scenarios around the ERG base case that applies the dostarlimab Weibull OS curve and ERG base case retaining the company preferred dostarlimab generalised gamma OS curve

	ICER	
	Weibull	**Gen.Gamm.**
Base case	£79,714	£64,006
SA01a: Cessation at [redacted]	£81,853	£63,583
SA01b: Cessation at [redacted]	£83,990	£63,140
SA02a: [redacted] dostarlimab [redacted] continuing treatment	£73,411	£59,041
SA02b: [redacted] dostarlimab [redacted] continuing treatment	£83,336	£66,859
SA03a: Waning starts [redacted] after [redacted] cessation	£77,378	£60,153
SA03b: Waning starts [redacted] after [redacted] cessation	£75,813	£57,082
SA04a: Dostarlimab Gompertz TTD curve (old data)	£80,921	£64,733
SA04b: Dostarlimab log-logistic TTD curve (old data)	£75,198	£60,225
SA04c : Dostarlimab log-normal TTD curve	£76,679	£61,392
SA05: Dostarlimab KM TTD for 8 months	£75,457	£60,429
SA06: German QoL values	£79,263	£63,465
SA07: RWEQ treatment cycles adjustment	£80,083	£64,296
SA08: Reduced specialist nurse frequency	£79,290	£64,170
SA09a: 10 year time horizon	£90,563	£74,322
SA09b: 20 year time horizon	£81,822	£65,962
SA09c: 30 year time horizon	£79,911	£64,186
SA10a : Lower CI OS curve	£139k	£95,290
SA10b : Upper CI OS curve	£57,484	£50,177
SA11a : Lower CI all curves	£123k	£84,118
SA11b : Upper CI all curves	£64,477	£56,329
SA02a + SA03a	£71,029	£55,327
SA02a + SA03b	£69,448	£52,411
SA02b + SA03a	£81,338	£63,164
SA02b + SA03b	£80,040	£60,184
SA02a + SA03a + SA04c	£68,811	£53,432
SA02a + SA03b + SA04c	£67,282	£50,626
SA02b + SA03a + SA04c	£79,558	£61,603
SA02b + SA03b + SA04c	£77,777	£58,328

It can be noted that in the above the scenario of SA02a + SA03b + SA04c and its ICER of £50,626 per QALY is the closest scenario the ERG presents to the company TE base case without company waning with its associated ICER of £49,608 per QALY. Removing the GARNET number of subsequent treatments multiplier and retaining the company preferred quality of life model further revises the SA02a + SA03b + SA04c scenario ICER to £49,795 per QALY and near complete alignment with the company TE estimate.

6.2 *ERG exploratory analyses against single RWEQ comparators*

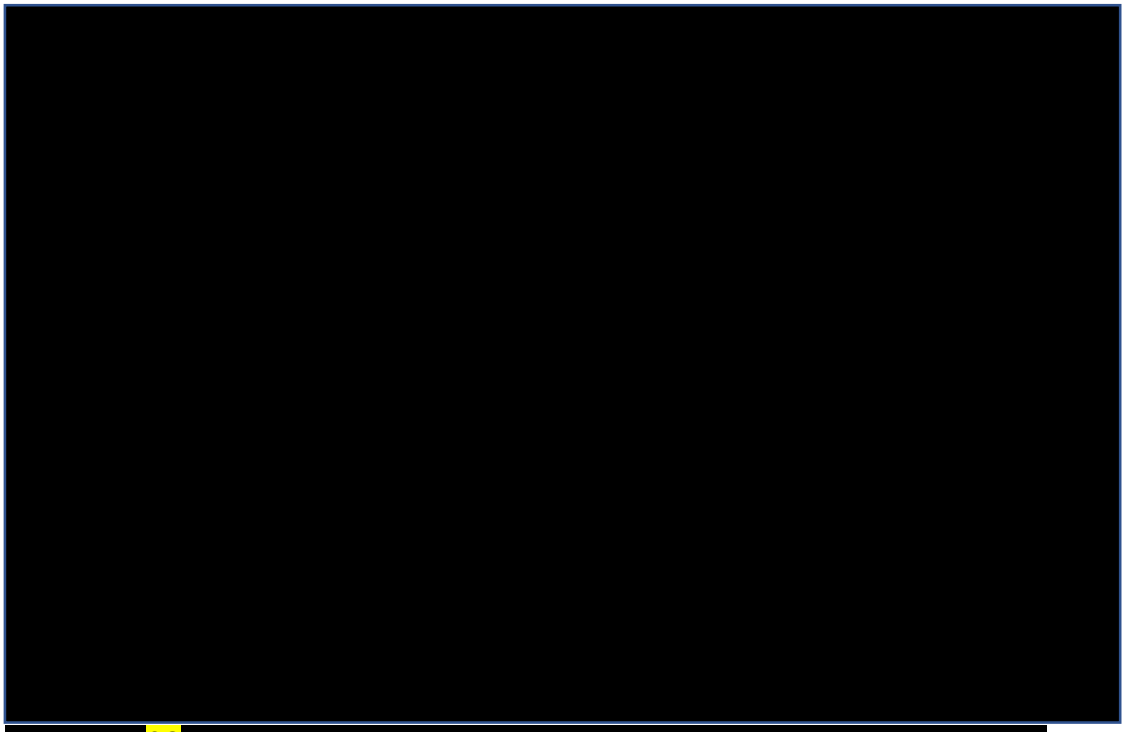
The ERG has fitted curves to the RWEQ individual treatment KM data for carboplatin + paclitaxel, carboplatin + PLD and PLD monotherapy. The ERG prefers the log-logistic parameterisation for these, with the exception of preferring the Weibull for the carboplatin + PLD TTD curve. This latter choice has little effect upon model outputs due to the company model limiting treatment to a maximum of [redacted] model cycles.

These can be used to estimate the cost effectiveness of dostarlimab against the individual treatments. A modelling issue arises as to whether the waning of effect for dostarlimab should be based upon the pooled RWEQ curves or upon the curves of the individual RWEQ treatment that is under consideration. The ERG will present the results of both approaches.

The ERG parameterised curves for the individual treatments are presented below in Xxxxxxx36, Xxxxxxx37 and Xxxxxxx38.

36

37



38

The cost effectiveness estimates for these are presented in Table 55.

Table 55: ERG RWEQ single treatment scenarios

Waning	RWEQ curves used			Comparator curves used		
Comparator	Δ QALY	Δ Cost	ICER	Δ QALY	Δ Cost	ICER
Carb+PAC	[redacted]	[redacted]	£104k	[redacted]	[redacted]	£108k
Carb+PLD	[redacted]	[redacted]	£88,929	[redacted]	[redacted]	£102k
PLD mono	[redacted]	[redacted]	£53,080	[redacted]	[redacted]	£58,120

What is perhaps most noteworthy is how much better the cost effectiveness estimate is for PLD monotherapy compared to the ERG base case of £79,714 per QALY: an improvement of 27-34%.

The company scenario analysis that compares dostarlimab with doxorubicin using the Zoptec trial suggests an ICER that is 25% worse than the company base case.

The ERG views the Zoptec trial as the most reliable of the company comparisons with doxorubicin. This may raise questions about patient recruitment during GARNET and Zoptec, how this compares with the RWEQ patient group and whether the comparison of GARNET with the RWEQ patient group may be biased.

The other company scenario analyses that compare dostarlimab with doxorubicin suggest ICERs that are 10% above, 18% below and 19% below the company base case ICER. None approach being below the base case ICER by the 27-34% of the ERG exploratory analyses.

7 END OF LIFE

Based on survival benefit estimated by the company (see CS section B.2.4.6), dostarlimab appears to meet the NICE efficacy criteria of extending life (more than 3 months survival than the current clinical management, and current clinical management survival of less than 24 months) for patients with recurrent or advanced EC that has progressed on or after platinum-based chemotherapy. However, there is uncertainty around the survival estimates as GARNET's data is immature and there are many issues surrounding data for comparators and longer-term outcomes beyond two years.

The company model estimates the following undiscounted life years. There may be some concerns around whether the values for the comparator arm are underestimates given the company experts' opinions as summarised in section ERG report section 4.2.6.3.

Table 56: Modelled undiscounted mean survival

Preferred assumption	RWEQ	DOST	Net
Company base case	[redacted]	[redacted]	[redacted]
ERG corrected company base case	[redacted]	[redacted]	[redacted]
ERG base case	[redacted]	[redacted]	[redacted]

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9 Appendix

9.1 *ERG assessment of the company SLR and included clinical studies*

Table 57: ERG ROBIS assessment of risks of bias of the CS systematic review of clinical effectiveness

ROBIS domain, and signalling questions	ERG's assessment of whether criteria met, with comments
DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	**Probably Yes**. No pre-published protocol, unclear if the changes made to searches (CS Appendix D.2) at the update were made *a priori*. The same eligibility criteria was used for the original and update clinical SLR (CS Appendix D.1 Table 1). A date limit was not set for the eligibility criteria; however, a date limit was applied to the MEDLINE and Embase update searches which means that older (pre-2018) may have been missed (particularly for paclitaxel studies and some systematic reviews study designs which were included search terms in the update SLR). However, this is mitigated by the fact that the Cochrane Library update and trials register searches were not date limited.
1.2 Were the eligibility criteria appropriate for the review question?	**Probably Yes**. The criteria presented in CS Appendix D.1 Table 1 are appropriate for the review question. The company did not consider hormone therapy (which was within the NICE final scope) as one of the comparators included in the original or update clinical SLR. However, the company provided a targeted literature review (TLR) for hormone therapy (CS Appendix L). The review followed the same eligibility criteria of the clinical SLR. No studies from the hormone therapy TLR was included in the economic evaluation. No additional relevant studies were identified by the ERG. A scenario analysis was conducted with hormone therapy, using the UK RWE study as a proxy to validate the base-case.
1.3 Were eligibility criteria unambiguous?	**Yes**. Eligibility criteria were unambiguous.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	**Probably Yes**. Most of the restrictions were appropriate. However, a reason for limiting sample size to ≥ 20 patients for observational studies was not provided. It is unclear whether this is appropriate.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	**Yes**. No language restrictions were applied.

Domain 1 risk of bias	**Low concern**
DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	**Yes.** Searched MEDLINE, Embase and Cochrane (CDSR and CENTRAL), ClinicalTrials.gov and EU clinical trials register (CS Appendix D.2).
2.2 Were methods additional to database searching used to identify relevant reports?	**Yes.** Hand searching of some relevant conferences and websites was undertaken.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	**Yes**. Full searches are reported for database sources. A variety of terms were used for each concept and these were combined correctly. However, the update search strategy is different in parts to the original searches, focussing on fewer interventions/comparators (reflecting those in the CS decision problem, except for hormone therapy), but with a broader population (EC rather than recurrent or advanced EC) and with other study types included. Terms for paclitaxel and systematic reviews are included in the update searches, but not in the original searches. The date limit applied to the MEDLINE and Embase update searches means that older (pre-2018) paclitaxel studies and some systematic reviews may have been missed, although this is mitigated by the fact that the Cochrane Library update and trials register searches were not date limited.
2.4 Were restrictions based on date, publication format, or language appropriate?	**Yes**. There are no restrictions on publication format or language in the search strategies. Date limits are appropriate, but note issue of older (pre 2018) paclitaxel studies and systematic reviews in 2.3 above
2.5 Were efforts made to minimise errors in selection of studies?	**Yes.** Title/abstract screening and full text screening for the wider SLR were undertaken by two reviewers. For title/abstract screening, where there was disagreement about the relevance of a study, it was progressed to full text screening. For full text screening, where there was disagreement about the relevance of a study, reasons for inconsistencies were discussed, if an agreement was not reached, a third reviewer was invited to make a judgment.
Domain 2 risk of bias	**Low concern**
DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
3.1 Were efforts made to minimise error in data collection?	**Yes**. Pre-defined extraction form used, extraction by two reviewers and verification by a third reviewer.
3.2 Were sufficient study characteristics available for both review authors	**Yes**. Characteristics of the thirteen studies meeting the eligibility criteria were presented by the company (CS Appendix D.4.3).

and readers to be able to interpret the results?	
3.3 Were all relevant study results collected for use in the synthesis?	**Yes**. CS Appendix D.4 (table 20 to table 28).
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	**Probably Yes.** Methodological quality was assessed using Appendix C of PMG6 refers - methodology checklist for randomised controlled trials in the old NICE guidelines manual) for RCTs, CASP check list for Non-RCTs, and ROBINS I assessment tool for the UK RWE study (CS section B.2.3.1.4 and Appendix D.7). These are not the tools preferred by NICE. The CS does not justify using a non-preferred checklist. The ERG quality assessed the studies using both the company's preferred checklist and the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) checklist for RCTs; and both the company's preferred checklist and the Institute of Health Economics checklist for Non-RCTs (including the UK RWE study). The ERG had some differences with the company's judgements (CS section B.2.3.1.4 and Appendix D.7 (see ERG report section 3.1).
3.5 Were efforts made to minimise error in risk of bias assessment?	**Yes**. Assessments by two reviewers, and reasons for disagreements were discussed and verified. Individual study authors were contacted for missing or incomplete information.
Domain 3 risk of bias	**Low concern**
DOMAIN 4: SYNTHESIS AND FINDINGS	
4.1 Did the synthesis include all studies that it should?	**No**. One study (Lissoni *et al* 1996) was excluded from the SLR (CS Appendix D.4.2 Table 14), but the ERG does not consider it as a previously identified paper and recommends its inclusion. However, the study is not eligible for the MAICs as PFS or OS data is not reported and therefore not important for economic evaluation.
4.2 Were all predefined analyses followed or departures explained?	**No information**. Pre-defined analyses not specified in the CS.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	**Probably Yes**. Results from different studies were described narratively. No meta-analysis was undertaken.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	**Probably No**. Heterogeneity was not explicitly discussed by the CS. However, the company aimed to generate a dataset for the comparator that was aligned with the patient population of GARNET.

4.5 Were the findings robust, e.g., as demonstrated through funnel plot or sensitivity analyses?	**Probably Yes**. Results from different studies were described narratively. The author discussed some studies that may be problematic.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	**Probably No**. Biases were assessed using the company's preferred tools (CS section B.2.3.1.4 and Appendix D.7). Most of the Non-RCT studies had a high risk of bias, while the RCTs mostly had a low risk of bias. The ERG had some differences with the company's judgements (CS section B.2.3.1.4 and Appendix D.7 (see ERG report section 3.1). The quality of the studies were highlighted in the findings or conclusions of the review.
Domain 4 risk of bias	**Unclear concern**
Overall risk of bias in the review	
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	**No.** The company did not addressed heterogeneity in study results in their analysis. In addition, the company did not provide information on predefined analyses in an explicitly referenced protocol or in the submission.
B. Was the relevance of identified studies to the review's research question appropriately considered?	**Yes**. Studies included were relevant to the objective and inclusion / exclusion criteria. The relevance of the included studies was also highlighted as part of the individual study quality assessment.
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	**Probably No**. There was no bias in the reporting of the findings from the review.
Risk of bias in the review	**Low risk of bias with some concern**

ERG summary assessment of risks of bias of the clinical effectiveness, Hormone Therapy Targeted Literature Review

The company did not initially consider hormone therapy (which was within the NICE final scope) as one of the comparators, and thus was not included in the original or update clinical SLR. However, the company provided a targeted literature review (TLR) for hormone therapy (CS Appendix L). The review followed the same eligibility criteria of the clinical SLR; however, efforts made to minimize errors in selection of studies during title/abstract or full text screening were not reported. All articles screened at full text stage were initially excluded and then re-evaluated with a relaxed set of inclusion criteria, in the effort to identify for hormone therapy (CS Appendix L.5). The ERG notes that it is uncertain whether any other records excluded at title/abstract screening would have met these relaxed criteria. No studies from the hormone therapy TLR were found relevant by the company for this submission; thus, none was included in the cost-effectiveness analysis. A scenario analysis was conducted with hormone therapy, using the UK RWE study as a proxy to validate the base-case.

Table 58: ERG and company assessment of RCT risk bias (Appendix C of PMG6 refers - methodology checklist for randomised controlled trials in the old NICE guidelines manual)

		ZoptEC ERG		ZoptEC CS	
A. Selection bias (systematic differences between the comparison groups)					
A1	An appropriate method of randomization was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	Patients were randomized in a 1:1 ratio to receive treatment with either AEZS-108 (Arm A) or doxorubicin (Arm B).	Yes	Centrally randomised
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes	Yes, participants were randomly allocated by central randomisation.	Unclear	Centrally randomised but otherwise not reported
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	Baseline demographics were similar for treatment groups.	YES/PARTIAL	Similar for age, race, ECOG and stage
Likely direction of effect			**Low risk of bias**	**Low risk of bias,** There appeared to be low risk for systematic differences between comparison groups	
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Unclear	It is unclear whether concurrent treatment administration was balanced across intervention groups.	Yes	The groups appeared to receive the same care
B2	Participants receiving care were kept 'blind' to treatment allocation	No	Open label study.	No	Open label.
B3	Individuals administering care were kept 'blind' to treatment allocation	No	Open label study.	No	Open label.
Likely direction of effect			**High risk of bias**	**High risk of bias,** Although this was an open label trial, the outcomes were objective.	
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted	Yes	There is a standard follow-up protocol for all patients.	Yes	The final analysis, which was event-based, was conducted

	to allow for differences in length of follow-up)				after approximately 384 randomised patients had died
C2	a. How many participants did not complete treatment in each group?		Not reported.		
C2	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Unclear	No information on dropouts.	Yes	13/256 vs. 15/255 did not complete
C3	a. For how many participants in each group were no outcome data available?		There were missing outcome reports for PFS for 10 participants (that is patients allocated to a treatment but never treated). 4 patients in AEZS-108 /Zoptarelin Doxorubicin group, and 6 patients in Doxorubicin group.		
C3	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	Unclear	It is unclear whether there are any important differences between those with and without outcome data in both intervention groups.	Yes	Analysis performed in the ITT or mITT (Excluding patients allocated to a treatment but never treated)
Likely direction of effect			**Unclear**	**Low risk of bias,** There was a low risk of attrition bias	
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	Yes, 3.87 years overall study follow-up period from start date – August 2013 to completion – January 30,2017.	Yes	Yes, the OS and PFS data were mature
D2	The study used a precise definition of outcome	Yes		Yes	The primary endpoint was OS, and other endpoints included PFS, ORR and CBR
D3	A valid and reliable method was used to determine the outcome	Yes	Standardised measurements were used to assess the outcomes. Response and progression were	Yes	Standard outcomes for OS, PFS and ORR were evaluated

			evaluated using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Adverse events (AEs) were assessed according to the National Cancer Institute CTCAE version 4.03 or subsequent ones.		
D4	Investigators were kept 'blind' to patients' exposure to the intervention	No	Open label study.	No	Open label study.
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	No	Open label study.	No	Open label study.
Likely direction of effect			**Unclear**	**Low risk of bias,** Although this was an open label trial, the outcomes were objective	

		McMeekin et al 2015 ERG		**McMeekin et al 2015 CS**	
A. Selection bias (systematic differences between the comparison groups)					
A1	An appropriate method of randomization was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	Patients were randomized in a 1:1 ratio to ixabepilone or either paclitaxel or doxorubicin, depending on prior therapy received.	Unclear	Not reported.
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Unclear	It is unclear whether treatment group allocation was concealed.	Unclear	Not reported.
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	Baseline demographics were similar for randomised patients in the ixabepilone and control arms.	Yes	Prognostic factors appear balanced at baseline.
Likely direction of effect			**Unclear**	**Unclear,** Methods of randomisation were unclear	
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					

B1	The comparison groups received the same care apart from the intervention(s) studied	Unclear	It is unclear whether concurrent administration of hormone replacement therapy were balanced across intervention groups.	Yes	
B2	Participants receiving care were kept 'blind' to treatment allocation	No	Open label study.	No	Open label study.
B3	Individuals administering care were kept 'blind' to treatment allocation	No	Open label study.	No	Open label study.
Likely direction of effect			**Unclear**	**High risk of bias,** Although this was an open label trial, the outcomes were objective	
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Unclear	All participants were followed up for at least 6 months.	Yes	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. If the follow-up on 300 patients occurred first, a minimum number of 160 deaths were required before conducting the futility analysis
C2	a. How many participants did not complete treatment in each group?		As at database lock date, a very high number of participants had dropped out of the study treatments (209 in the ixabepilone arm and 210 in the control arm).		
C2	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Unclear	It is unclear if there are any significant differences between those who dropped out and those who stayed on treatment.	Yes	At the time of database lock (DBL; February 8, 2012), 419 patients were off study treatment, 209 in the ixabepilone arm and 210 in the control arm. The most common reason for treatment discontinuation was

					disease progression (52% of ixabepilone patients and 53% of control patients) and study drug toxicity (14% of ixabepilone patients and 7% of control patients).
C3	a. For how many participants in each group were no outcome data available?		There were missing outcome reports for PFS and ORR for 25 participants in each group.		
C3	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	Unclear	Outcome reports for PFS and ORR was not reported for equal number of patients in both groups - 25 participants in each group. It is unclear whether there are any important differences between those with and without outcome data in both intervention groups.	Yes	Efficacy was reported in all randomised patients
Likely direction of effect			**Unclear**	**Low risk of bias**	
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	Yes, 29.6 months overall study follow-up period from start date – August 17, 2009.	Yes	Yes, the OS and PFS data were mature
D2	The study used a precise definition of outcome	Unclear	The definition of outcomes were not noted.	Yes	The primary endpoint was OS, and other endpoints included PFS and ORR
D3	A valid and reliable method was used to determine the outcome	Yes	Standardised measurements were used to assess the outcomes. Response and disease progression were evaluated using Response Evaluation Criteria in Solid Tumors, version 1.1. Adverse events (AEs), laboratory values, and other signs and symptoms were assessed according to the National Cancer Institute CTCAE version 3.0.	Yes	Standard outcomes for OS, PFS and ORR were evaluated

D4	Investigators were kept 'blind' to patients' exposure to the intervention	No	Open label study.	No	Open label study.
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	No	Open label study.	No	Open-label
Likely direction of effect			**Unclear**	**Low risk of bias,** Although this was an open label trial, the outcomes were objective.	

Table 59: ERG and company assessment of non-RCT risk of bias (CASP cohort study checklist)

Section A: Are the results of the study valid?	GARNET ERG	GARNET CS
1. Did the study address a clearly focused question issue?	Yes The objective of the study was "to evaluate the antitumor activity of dostarlimab in participants with recurrent and advanced dMMR/MSI-H EC, in terms of ORR and DOR by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)"".	Yes Objective: To evaluate the antitumour activity of dostarlimab in subjects with recurrent and advanced dMMR/MSI-H EC, in terms of ORR and DOR by BICR using RECIST v1.1
2. Was the cohort recruited in an acceptable way?	Can't Tell CS section B.2.3.1.1, and Appendix P.1	Yes Patients were recruited from 117 sites in 9 countries as part of this multicentre, global clinical trial according to pre-defined eligibility criteria
3. Was the exposure accurately measured to minimise bias?	Yes Patient Baseline Characteristics were accurately classified, such as FIGO disease stage at diagnosis, histology, type and number of prior lines of therapy were presented.	Yes Standard, validated, objective measurements were evaluated including ORR, DOR, DCR, PFS.
4. Was the outcome accurately measured to minimise bias?	Yes CS section B.2.3.1	Yes Outcomes were assessed by BICR according to RECIST criteria
5a. Have the authors identified all important confounding factors?	Not applicable	Yes/Partial Predefined subgroup data cross some factors
5b. Have they taken account of the confounding factors in the design and/or analysis? Or Could there	Not applicable Descriptive statistics	Yes/Partial Predefined subgroup data cross some factors

be confounding factors that haven't been accounted for?		
6a. Was the follow up of subjects complete enough?	Can't Tell CS Appendix D.6 table 64	Yes Follow-up was sufficiently recorded: The most common reason for treatment discontinuation was PD; Most of the study discontinuations were because of death
6b. Was the follow up of subjects long enough?	No Not for whole sample. As at the time of Cut-off for analysis March 1, 2020, the median in study follow-up time was 16.3 months; median Duration of response (DOR) and median OS was not reached.	No Median OS was immature; however the follow-up was long enough to determine the other outcomes
Section B: What are the results?	**GARNET ERG**	**GARNET CS**
7. What are the results of this study?	- CS section B.2.4	
8. How precise are the results?	- Confidence intervals (CIs) reported for all outcomes except adverse events.	Yes/Partial 95% CIs were generally within a reasonable range; some of the smaller subgroups are large intervals
9. Do you believe the results?	Can't tell Study was unblinded, and single-arm with small sample size. The results should be interpreted with caution.	Yes Evaluated by BICR under clinical trial conditions
Section C: Will the results help locally?	**GARNET ERG**	**GARNET CS**
10. Can the results be applied to the local population?	Can't Tell Study was unblinded, and single-arm with small sample size. The results must be interpreted with caution.	Yes/Partial A global multicentre study with generally good generalisability; however, the majority of patients were White so may not be relevant to some populations

11. Do the results of this study fit with other available evidence?	Can't Tell No published studies for dostarlimab in recurrent or advanced EC is available.	Unclear No other published studies for dostarlimab in EC
12. What are the implications of this study for practice?	Can't Tell Implications for Practice "Study results from this interim analysis (IA-2) demonstrate that dostarlimab treatment results in durable responses in a substantial proportion of participants with recurrent or advanced dMMR or dMMR/MSI-H EC". Study was unblinded, and single-arm with small sample size. Difficult to draw conclusion because of study design.	Unclear Clinical trial evidence for dostarlimab in EC; however not an RCT & therefore the extent of benefit vs. other treatments is not clear

Section A: Are the results of the study valid?	Makker et al 2013 ERG comments	Makker et al 2013 CS comments
1. Did the study address a clearly focused question issue?	Yes The objective of the study was "To determine the efficacy of second-line doxorubicin in the treatment of advanced/recurrent endometrial carcinoma that has progressed after adjuvant paclitaxel/carboplatin (TC) therapy among patients treated at MSKCC between 1995 and 2009."	Yes Objective: To investigate the activity of doxorubicin in the second-line setting in patients who progressed after paclitaxel/carboplatin adjuvant treatment
2. Was the cohort recruited in an acceptable way?	No Retrospective study. Participants were recruited from electronic medical records.	No Single centre, retrospective study
3. Was the exposure accurately measured to minimise bias?	Yes CS Appendix D.4.3	Yes Standard, validated, objective measurements were evaluated including ORR by RECIST criteria, OS and PFS
4. Was the outcome accurately measured to minimise bias?	Yes RECIST v1.1 was used. Toxicity was assessed version 4.0 of Common Terminology Criteria for Adverse Events (CTCAE).	Unclear Response was defined according to standard RECIST criteria; not clear if blinded
5a. Have the authors identified all important confounding factors?	Not applicable	Unclear NR
5b. Have they taken account of the confounding factors in the design and/or analysis? Or Could there be confounding factors that haven't been accounted for?	Not applicable Descriptive Statistics.	Unclear NR

6a. Was the follow up of subjects complete enough?	Can't Tell It is unclear if the excluded 8 subjects will have different outcomes than those assessed.	No Follow-up not reported
6b. Was the follow up of subjects long enough?	Can't Tell Only noted the follow-up duration of the one patient alive after receiving the doxorubicin treatment (49.4 months).	Yes The follow-up was sufficient for the outcomes assessed
Section B: What are the results?	**Makker et al 2013 ERG comments**	**Makker et al 2013 CS comments**
7. What are the results of this study?	- CS Appendix D.4	
8. How precise are the results?	- Confidence intervals (CIs) reported for all outcomes except adverse events. CIs were large for all outcomes.	Yes 95% CIs were generally within a reasonable range
9. Do you believe the results?	Can't tell Study was unblinded, retrospective, with patient selection bias and small sample size. The results should be interpreted with caution.	Yes/Partial Results appear reliable, although small population <30
Section C: Will the results help locally?	**Makker et al 2013 ERG comments**	**Makker et al 2013 CS comments**
10. Can the results be applied to the local population?	Can't Tell Study was unblinded, and single-arm with a small sample size. The results must be interpreted with caution.	Unclear Patients from single centre in US
11. Do the results of this study fit with other available evidence?	Yes CS Appendix D.4	Unclear Only a few similar studies

12. What are the implications of this study for practice?	Yes Implications for Practice “Doxorubicin may be considered inactive as second-line therapy in this endometrial carcinoma population.”	No Single arm, single centre, retrospective study; small patient population

Section A: Are the results of the study valid?	**Mazgani et al 2008 ERG comments**	**Mazgani et al 2008 CS comments**
1. Did the study address a clearly focused question issue?	Yes The objective of the study was “To evaluate the efficacy of reusing carboplatin and paclitaxel (taxol) in women with relapsed endometrial cancer.”	Yes Objective: To evaluate the efficacy of reusing carboplatin and taxol in women with relapsed EC
2. Was the cohort recruited in an acceptable way?	No Participants were selectively recruited.	No Single centre, retrospective study
3. Was the exposure accurately measured to minimise bias?	Yes Patient were accurately classified into endometroid and papillary serous histology groups.	Yes Objective measurements were evaluated including response, OS, PFS
4. Was the outcome accurately measured to minimise bias?	Can’t Tell Response Confirmatory measure deviated from RECIST criteria.	Unclear Response was defined according to standard RECIST criteria; not clear if blinded
5a. Have the authors identified all important confounding factors?	Can’t Tell Not reported.	Unclear Not reported.
5b. Have they taken account of the confounding factors in the design	Can’t Tell	Unclear

and/or analysis? Or Could there be confounding factors that haven't been accounted for?	Not reported.	Not reported.
6a. Was the follow up of subjects complete enough?	Can't Tell Not reported.	No Follow-up not reported
6b. Was the follow up of subjects long enough?	Can't Tell Not reported.	Yes The follow-up was sufficient for the outcomes assessed
Section B: What are the results?	**Mazgani et al 2008 ERG comments**	**Mazgani et al 2008 CS comments**
7. What are the results of this study?	- CS Appendix D.4.4, D.4.5, D.4.6	
8. How precise are the results?	- Confidence intervals (CIs) were reported for most outcomes. CIs were wide for most outcomes, particularly for outcomes related to papillary serous histology subgroup.	Unclear 95% CIs not reported for all outcomes; reasonable range for some but large for serous histology subgroup (small population size)
9. Do you believe the results?	Can't tell Study was unblinded, retrospective, with patient selection bias and small sample size. The results should be interpreted with caution.	Yes/Partial Results appear reliable, although small population <30
Section C: Will the results help locally?	**Mazgani et al 2008 ERG comments**	**Mazgani et al 2008 CS comments**
10. Can the results be applied to the local population?	Can't Tell Study was unblinded, and single-arm with a small sample size. The results must be interpreted with caution.	Unclear Patients from single centre in Canada/baseline characteristics NR
11. Do the results of this study fit with other available evidence?	Yes	Unclear

	CS Appendix D.4 According to the Authors “Other than in the case series of Markman et al. who described 3 patients who had relapsed metastatic endometrial cancer with persistent chemosensitivity to platinumand/or paclitaxel,we were unable to find any other data on the reuse of carboplatin–taxol in relapsed endometrial cancer in the English language literature”. However, this study fits well with studies including other types of chemotherapies.	Author states there are no other studies about reuse of carboplatin–taxol in relapsed EC in the English language literature
12. What are the implications of this study for practice?	Yes Implications for Practice “Carboplatin–taxol regimen is an efficacious treatment. Due to the patient selection these outcomes reported are likely to be an overstatement of what could be achieved in practice.” Study was unblinded, retrospective, with patient selection bias and small sample size. Difficult to draw conclusion because of study design.	No Single arm, single centre, retrospective study

Section A: Are the results of the study valid?	**Rubinstein et al 2019 ERG comments**	**Rubinstein et al 2019 CS comments**
1. Did the study address a clearly focused question issue?	Yes The objective of the study was “To determine the efficacy of second-line doxorubicin in the treatment of advanced/recurrent endometrial carcinoma that has progressed after	Yes Objective: To examine the clinical outcomes of EC patients who received PC in the adjuvant setting and who were specifically re-treated with PC in the recurrent or metastatic disease setting

	adjuvant paclitaxel/carboplatin (TC) therapy."	
2. Was the cohort recruited in an acceptable way?	No Retrospective study. Participants were recruited from an institutional database.	No Single center, retrospective study
3. Was the exposure accurately measured to minimise bias?	Yes CS Appendix D.4.3.	Yes Standard, validated, objective measurements were evaluated including response (RECIST), OS and PFS
4. Was the outcome accurately measured to minimise bias?	Yes RECIST v1.1 was used.	Yes An independent radiologist, blinded to patients' clinical details assessed response per RECIST 1.1 criteria
5a. Have the authors identified all important confounding factors?	Not applicable	Unclear Some baseline prognostic factors are not reported & data not reported by prognostic/confounders
5b. Have they taken account of the confounding factors in the design and/or analysis? Or Could there be confounding factors that haven't been accounted for?	Not applicable Descriptive Statistics.	Unclear Not reported
6a. Was the follow up of subjects complete enough?	Can't Tell It is unclear if the excluded 5 subjects will have different outcomes than those assessed.	No Follow-up not reported
6b. Was the follow up of subjects long enough?	Can't Tell No information.	Yes The follow-up was sufficient for the outcomes assessed

Section B: What are the results?	Rubinstein et al 2019 ERG comments	Rubinstein et al 2019 CS comments
7. What are the results of this study?	- CS Appendix D.4	
8. How precise are the results?	- Confidence intervals reported for most outcomes. Reported CIs were wide.	No 95% CIs not reported for all outcomes; quite large range for some outcomes
9. Do you believe the results?	Can't tell Study was unblinded, retrospective, with patient selection bias and small sample size. The results should be interpreted with caution.	Yes/Partial Results appear reliable, although small population <30
Section C: Will the results help locally?	**Rubinstein et al 2019 ERG comments**	**Rubinstein et al 2019 CS comments**
10. Can the results be applied to the local population?	Can't Tell Study was unblinded, and single-arm with a small sample size. The results must be interpreted with caution.	Unclear Patients from single centre in Canada/baseline characteristics NR
11. Do the results of this study fit with other available evidence?	Yes CS Appendix D.4.	Unclear Only a few similar studies
12. What are the implications of this study for practice?	Yes Implications for Practice "selected patients with recurrent endometrial cancer (EC) who are >6 months from completion of paclitaxel and carboplatin (PC) derive benefit from retreatment with PC with a response rate of 50%."	No Single arm, single centre, retrospective study, small population

Section A: Are the results of the study valid?	Julius et al 2013 ERG comments	Julius et al 2013 CS comments
1. Did the study address a clearly focused question issue?	Yes The objective of the study was "To determine factors which may increase the likelihood of adverse drug events (ADEs) in recurrent endometrial cancer patients treated with pegylated liposomal doxorubicin (PLD) as well as this agent's impact on clinical outcomes."	Yes Objective: To determine factors which may increase the likelihood of ADEs in recurrent EC patients treated with pegylated liposomal doxorubicin
2. Was the cohort recruited in an acceptable way?	No Retrospective study. Participants were recruited from a medical records database.	No Single center, retrospective study
3. Was the exposure accurately measured to minimise bias?	Yes CS Appendix D.4.3	No Objective measures OS and PFS & TTP evaluated; response was an outcome but was not reported
4. Was the outcome accurately measured to minimise bias?	Can't Tell More detail is needed on the methods of outcomes assessment. E.g. what was the criteria used to assess radiographic evidence of response to therapy.	Unclear Limited details of evaluations.
5a. Have the authors identified all important confounding factors?	No Platinum sensitivity status was identified as an important confounding factor. However, other factors could have been noted, such as age, BMI, comorbidities, and race/ethnicity, number of prior	Unclear Some baseline prognostic factors are not reported & data not reported by prognostic/confounders

	chemotherapy, cycles of chemotherapy prior to receiving PLD, stage of disease, type of endometrial cancer histology classification, ECOG status e.t.c.	
5b. Have they taken account of the confounding factors in the design and/or analysis? Or Could there be confounding factors that haven't been accounted for?	No Other factors could have been noted, such as age, BMI, comorbidities, and race/ethnicity, number of prior chemotherapy, cycles of chemotherapy prior to receiving PLD, stage of disease, type of endometrial cancer histology classification, ECOG status e.t.c.	Unclear Not reported
6a. Was the follow up of subjects complete enough?	Can't Tell No information.	Yes Follow-up was sufficiently reported
6b. Was the follow up of subjects long enough?	Can't Tell Not reported.	Yes The follow-up was sufficient for the outcomes assessed
Section B: What are the results?	**Julius et al 2013 ERG comments**	**Julius et al 2013 CS comments**
7. What are the results of this study?	- CS Appendix D.4. Median overall PFS for all doses combined was not reported.	
8. How precise are the results?	- Confidence intervals were not reported.	Unclear 95% CIs not reported
9. Do you believe the results?	Can't tell Study was unblinded, retrospective, with patient selection bias and small sample size. The results should be interpreted with caution.	Yes/Partial Results appear reliable, although small population <30

Section C: Will the results help locally?	Julius et al 2013 ERG comments	Julius et al 2013 CS comments
10. Can the results be applied to the local population?	Can't Tell Study was unblinded, and single-arm with small sample size, heterogeneity of patients, and lack of dose diversity. The results must be interpreted with caution.	Unclear Patients from single centre in US
11. Do the results of this study fit with other available evidence?	Yes CS Appendix D.4	Unclear Only a few similar studies
12. What are the implications of this study for practice?	Yes Implications for Practice "this is one of the first studies to demonstrate benefit of PLD in recurrent endometrial cancer as well as that dose level did not significantly influence efficacy. This study confirmed cumulative dose/cycles did increase risk of toxicity with PLD, which is common with most cytotoxic agents. PLD remains a viable option for patients with recurrent or progressive endometrial cancer..."	No Single arm, single center, retrospective study; small patient population

Table 60: ERG and company assessment of UK RWE study risk of bias (The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool)

ROBINS-I tool (Stage I): At protocol stage		
Specify the review question CS		**ERG assessment**
Participants	English patients diagnosed with advanced or recurrent endometrial cancer who have progressed on or after first-line platinum doublet therapy, specifically a GARNET trial-like cohort i.e. application of the inclusion and exclusion criteria as per the GARNET TRIAL where possible	England residents with at least one incident primary diagnosis of advanced or recurrent endometrial cancer between 01/01/2013 and 31/12/2018 who must have received exactly one prior platinum doublet therapy for recurrent or advanced disease.
Experimental intervention	Current UK treatment paradigms as a basket of treatments, in the line directly post-platinum	Basket of common chemotherapy regimens.
Comparator	Not applicable	None
Outcomes	Survival outcomes – overall survival, time to next treatment and time to treatment discontinuation	Time to next treatment (TTNT) as a proxy for Progression free survival (PFS) FS and Overall survival (OS)
List the confounding domains relevant to all or most studies		**ERG assessment**
1. dMMR status 2. Race/ethnicity (Black, Others, Unknown vs. White) 3. Age category (≥65 years vs. <65 years) 4. ECOG status at treatment initiation (1 vs. 0) 5. Histology at initial diagnosis (Non-endometrioid, Unknown vs. Endometrioid) 6. Federation of Gynecology and Obstetrics (FIGO) Stage (Stage III/IV vs. Stage I/II) 7. Grade of disease at diagnosis (Grade 3/4, Unknown vs. Grade 1/2) 8. Number of prior platinum-based therapies (0 or 1 vs. ≥2) 9. Prior surgery for study indication (Yes vs. No)		1. Race/ethnicity (black, others, unknown versus white) 2. Age category (≥65 years versus <65 years) 3. ECOG PS status at treatment initiation (1 versus 0) 4. Histology at initial diagnosis (non-endometrioid, unknown versus endometrioid) 5. FIGO stage at initial diagnosis (Stage III/IV versus Stage I/II) 6. Grade of disease at diagnosis (Grade 3/4, unknown versus Grade 1/2) 7. Number of prior platinum-based therapies (0 or 1 versus ≥2) 8. Prior surgery for study indication (yes versus no) 9. dMMR/MSHI status
List co-interventions that could be different between intervention groups that could impact on outcomes		**ERG assessment**

• The systemic anti-cancer therapy (SACT) database collects data on systemic anti-cancer therapies only. No other pharmacological interventions would be captured within the study, which could impact on outcomes. • The study would also capture surgery and radiotherapy interventions.	• No co-intervention recorded in the patient-level UK health data available through the NCRAS where the UK RWE information was obtained.

ROBINS-I tool (Stage II): For each study		
Specify a target randomised trial specific to the study		**ERG assessment**
Design	Individually randomised – the trial would be designed as per the GARNET trial cohort 2A	Individually randomized study design
Participants	English patients diagnosed with advanced or recurrent endometrial cancer who have progressed on or after first-line platinum doublet therapy, specifically a GARNET trial-like cohort i.e. application of the inclusion and exclusion criteria as per the GARNET trial	England residents with primary diagnosis of advanced or recurrent endometrial cancer who must have received exactly one prior platinum doublet therapy for recurrent or advanced disease
Experimental intervention	Current UK treatment paradigms, as a basket of treatments and for each individual relevant treatment, in the line directly post-platinum	Basket of common chemotherapy regimens.
Comparator	Placebo	Placebo
Is your aim for this study…?		
To assess the effect of *assignment to* intervention	Yes	Yes
To assess the effect of *starting and adhering to* intervention	No	No
Specify the outcome *Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.*		**ERG assessment**
• Progression free survival (PFS) • Overall survival (OS) • These are a proposed benefit of the intervention		• Progression free survival (PFS) • Overall survival (OS) • Proposed benefit of the intervention
Specify the numerical result being assessed *In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.*		**ERG assessment**

• PFS - The time from date of first dose to the earlier date of assessment of progression or death by any cause in the absence of progression based on: (1) the time of first documentation of PD per RECIST v1.1 • OS - The time from date of first dose of study treatment to the date of death by any cause.	• PFS – time from the date of the first dose to the earlier date of assessment of disease progression or death by any cause in the absence of disease progression based on the time of first documentation of disease progression per RECIST v1.1. • OS - defined as the time from the date of the first dose of study treatment to the date of death by any cause.

ROBINS-I tool (Stage II): preliminary consideration of confounders

Confounding domain CS	**Confounding domain ERG assessment**	**Measured variable(s) CS**	**Measured variable(s) ERG assessment**	**Is there evidence that controlling for this variable was unnecessary?* CS**	**Is there evidence that controlling for this variable was unnecessary?* ERG assessment**	**Is the confounding domain measured validly and reliably by this variable (or these variables)? CS**	**Is the confounding domain measured validly and reliably by this variable (or these variables)? ERG**
dMMR status	dMMR/MSHI status	No – was not available in the data set	No - not reported	Influence of controlling for this variable was not explored in this descriptive study. Descriptive statistics on this variable were captured in the study	No - Not reported	No – dMMR/MSI-H biomarker data are available within the NCRD. Although the dMMR/MSI-H biomarker is not prognostic, not having complete information on this biomarke	No information

						r is a limitation.	
Race/ethnicity	Race/ethnicity	Yes - (Black, Others, Unknown vs. White)	Yes - Black, Others, Unknown vs. White	As above	No - CS section CS B.2.7.1; Appendix D.5.1	Yes	Yes – CS section CS B.2.7.1; Appendix D.5.1
Age	Age	Yes - (≥65 years vs. <65 years)	Yes - ≥65 years vs. <65 years	As above	Yes - CS section CS B.2.7.1; Appendix D.5.1	Yes	Yes - CS section CS B.2.7.1; Appendix D.5.1
ECOG status at treatment initiation	ECOG PS status at treatment initiation	Yes - (1 vs. 0)	Yes - 1 vs. 0	As above	Yes - CS section CS B.2.7.1; Appendix D.5.1	Partially - ECOG status is recorded at diagnosis in the database. This may introduce bias to the ECOG status of recurrent patients; the ECOG status recorded at stage I and II EC diagnosis may not represent the ECOG status experienced at recurrence.	No - CS section B.2.7.1; Appendix D.5.1. ECOG PS is recorded at registry diagnosis. This may not be appropriate for those with recurrent disease.
Histology at initial diagnosis	Histology at initial diagnosis	Yes - (Non-endomet	Yes - Non-endomet	As above	No - CS section CS B.2.7.1;	Yes	Yes - CS section CS

		rioid, Unknown vs. Endometrioid)	rioid, Unknown vs. Endometrioid		Appendix D.5.1		B.2.7.1; Appendix D.5.11
Federation of Gynecology and Obstetrics (FIGO) Stage	FIGO stage at initial diagnosis	Yes - (Stage III/IV vs. Stage I/II)	Yes - Stage III/IV vs. Stage I/II	As above	No - CS section CS B.2.7.1; Appendix D.5.1	Yes	Yes - CS section CS B.2.7.1; Appendix D.5.1
Grade of disease at diagnosis	Grade of disease at diagnosis	Yes - (Grade 3/4, Unknown vs. Grade 1/2)	Yes - Grade 3/4, Unknown vs. Grade 1/2	As above	Yes - CS section CS B.2.7.1; Appendix D.5.1	Yes	Yes - CS section CS B.2.7.1; Appendix D.5.1
Number of prior platinum-based therapies	Number of prior platinum-based therapies	Yes - (0 or 1 vs. ≥2)	Yes - 0 or 1 vs. ≥2	As above	No - CS section CS B.2.7.1; Appendix D.5.1	Yes	Yes - CS section CS B.2.7.1; Appendix D.5.1
Prior surgery for study indication	Prior surgery for study indication	Yes - (Yes vs. No)	Yes - Yes vs. No	As above	No - CS section CS B.2.7.1; Appendix D.5.1	Partially - Beyond the cancer registry, diagnosis and procedure recording in HES is poor for all but inpatient settings owing to limited clinician capacity. Accordingly, the reporting of factors dependent upon	No information

						hospital data, such as surgery, may select on more acute or serious healthcare events and fail to present a full picture of surgical treatment .	

ROBINS-I tool (Stage II): preliminary consideration of co-interventions

Co-intervention CS	**Co-intervention ERG assessment**	**Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? CS**	**Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? ERG assessment**	**Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator (CS)**	**Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator (ERG assessment)**
Surgery Radiotherapy	Not applicable	Influence of controlling for this intervention was not explored in this descriptive study. Descriptive statistics on this intervention were captured in the study	Not applicable	Favour experimental	No information

ROBINS-I tool (Stage II): risk of bias assessment

Signalling questions	Description CS	Description ERG	Response options CS	Response options ERG
Bias due to confounding				
1.1 Is there potential for confounding of the effect of intervention in this study? **If <u>N/PN</u> to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered **If Y/PY to 1.1:** determine whether there is a need to assess time-varying confounding:	• All the pre-intervention prognostic factors listed above could impact intervention received at start of follow up. • The study looks at a basket of chemotherapies, therefore the outcomes of patients will be captured regardless of intervention received. • The study only captures patient's post-platinum treatment, confounding factors could influence what patients received platinum treatment first line.	Only counts available (no adjustment for confounders).	Y	Y
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.	Analysis of survival outcomes in the post-platinum setting were not split according to intervention received, all chemotherapies were included in the basket.	Analyses were not split according to intervention received; all chemotherapy treatments were grouped together in one basket.	N	N
1.3. Were intervention discontinuations or				Not applicable

switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)				
Questions relating to baseline confounding only				
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	This observational descriptive study did not control for any confounding prognostic factors, it described the prognostic factors within the cohort and captured the entire cohort's survival outcomes.	Descriptive statistics. The study did not control for any confounding factors.	N	N
1.5. **If <u>Y/PY</u> to 1.4:** Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?			Not applicable	Not applicable
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	This observational descriptive study did not control for any post-intervention variables, it described the entire cohort's survival outcomes.	Descriptive statistics. The study did not control for any confounding factors.	<u>N</u>	<u>N</u>
Questions relating to baseline and time-varying confounding				
1.7. Did the authors use an appropriate analysis method that	This observational descriptive study did not control for any	Descriptive statistics. The study did not	N	N

controlled for all the important confounding domains and for time-varying confounding?	confounding prognostic factors, it described the prognostic factors within the cohort and captured the entire cohort's survival outcomes.	control for any confounding factors.		
1.8. **If <u>Y/PY</u> to 1.7:** Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?				Not applicable
Risk of bias judgement				
Optional: What is the predicted direction of bias due to confounding?	This observational descriptive study did not control for any confounding prognostic factors. The study was designed to capture a real work UK advanced recurrent endometrial cancer population, adjusting for any prognostic variables within this cohort would decrease the generalizability of the cohort to a typical UK cohort. An indirect treatment comparison using matched adjusted indirect comparison methodology has been used to control for confounding, when comparing the outcomes described in this study versus the outcomes observed for patients treated with dostarlimab in the GARNET trial.	Descriptive statistics. The study did not control for any confounding factors.	No information Unpredictable	No information Unpredictable
Bias in selection of participants into the study				

2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4	All patients with survival outcomes data who received a treatment in the line directly post-platinum were included in the study cohort. Survival outcomes were tracked from the chemotherapy given directly post-platinum. No patient characteristics observed after the start of the intervention affected patient selection.	CS section B.3.2	N	N
2.2. **If Y/PY to 2.1:** Were the post-intervention variables that influenced selection likely to be associated with intervention?				Not applicable
2.3 **If Y/PY to 2.2:** Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?				Not applicable
2.4. Do start of follow-up and start of intervention coincide for most participants?	Start of follow up for the patient begin at entry into the NCRAS database, based on the date of endometrial cancer diagnosis; therefore, in advance of start of intervention for participants.	CS section B.3.2	Y	Y
2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4:** Were adjustment techniques used that are likely to correct for the presence of selection biases?				Not applicable
Risk of bias judgement				

Optional: What is the predicted direction of bias due to selection of participants into the study?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Low	Low
Bias in classification of interventions				
3.1 Were intervention groups clearly defined?	SACT contains detailed systemic treatment data for patients treated or funded by the National Health Service (NHS). All treatments captured in SACT aligned to this patient population and tumour of interest were included.	CS section B.3.2	Y	Probably Yes
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes. All SACT therapies were to be included.	CS section B.3.2	Y	Y
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No. All interventions are included within the SACT database, separate to information regarding outcomes.	All of the basket of chemotherapy recorded were obtained independent of the pre-defined outcomes.	N	N
Risk of bias judgement				
Optional: What is the predicted direction of bias due to classification of interventions?	Treatments in primary care are not included. As such, some oral and hormone therapies may be underreported, as is perhaps evident in the near total absence of hormone therapy delivery identified for the GARNET-like population Favours experimental / Favours comparator	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Moderate	Moderate

	/ Towards null /Away from null / Unpredictable			
Bias due to deviations from intended interventions				
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2				
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	All patients captured within the post-platinum patient cohort were required to receive a post-platinum treatment as recorded in SACT.	There is insufficient information on the administration of the basket of therapies.	N	No information
4.2. **If Y/PY to 4.1:** Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?				Not Applicable
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6				
4.3. Were important co-interventions balanced across intervention groups?	Co-interventions, surgery and radiotherapy, was captured as a descriptive statistic for the entire patient cohort. The co-interventions are therefore used by some participants in the cohort and not others.		N	Not Applicable
4.4. Was the intervention implemented successfully for most participants?	All patients captured within the post-platinum patient cohort were required to receive a post-platinum treatment, for any duration, as recorded in SACT. Time on treatment was recorded also.		Y	Not Applicable
4.5. Did study participants adhere to the assigned intervention regimen?	All patients captured within the post-platinum patient cohort were required to receive a post-		Y	Not applicable

	platinum treatment, for any duration, as recorded in SACT. Time on treatment was recorded also.			
4.6. **If N/PN to 4.3, 4.4 or 4.5:** Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?				Not applicable
Risk of bias judgement				
Optional: What is the predicted direction of bias due to deviations from the intended interventions?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Moderate	No information
Bias due to missing data				
5.1 Were outcome data available for all, or nearly all, participants?	Although data completeness is high for most core items available within the NCRD, staging data were absent for around 9% of the 45,494 EC patients diagnosed between 2013 and 2018. Given that staging information was central to the derivation of the advanced or recurrent disease cohort, these patients could not be included. It is unlikely that tumour staging is missing completely at random, thereby introducing some degree of selection bias; missing staging data will typically relate to older patients with advanced disease and short survival from diagnosis, such that	CS section B. 2.4 Grade of disease at diagnosis and ECOG PS status were not reported for a substantial number of patients.	N	N

	pathology was never completed. ECOG status was not recorded for a large number of patients. Scenario analysis was completed to include patients ECOG≤1 only (to match the GARNET trial criteria) or include patients ECOG≤1 and not recorded patients.			
5.2 Were participants excluded due to missing data on intervention status?	Intervention status was available for all patients; SACT collect all data for intravenous chemotherapies administered in the NHS.	Intervention status was reported for all patients.	N	N
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Patients were excluded due to lack of staging data.	CS section B. 2.4 Participants were excluded based on no recorded stage at diagnosis.	Y	Y
5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3:** Are the proportion of participants and reasons for missing data similar across interventions?			NA	Not applicable
5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3:** Is there evidence that results were robust to the presence of missing data?	Scenario analysis was completed to include patients ECOG≤1 only (to match the GARNET trial criteria) or include patients ECOG≤1 and not recorded patients; survival outcomes form both groups were similar. The impact of including patients with missing staging data was not explored.	CS section B.2.7 and Appendix D.5.1 - scenario analyses	PN	Probably Yes

Risk of bias judgement				
Optional: What is the predicted direction of bias due to missing data?	The exclusion of patients with missing staging data was required to align the study cohort with the GARNET trial cohort, where disease stage was an inclusion criteria. Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	It is uncertain if the scenario analyses have removed the risk of bias arising from the missing data.	Moderate	Moderate Unpredictable
Bias in measurement of outcomes				
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Outcomes were mortality and time to next treatment as recorded in the databased, which would not be influenced by knowledge of intervention.	Outcome measures were retrieved as recorded in the database.	N	N
6.2 Were outcome assessors aware of the intervention received by study participants?	Outcomes were assessed using time to event data from the NCRAS data base.	Yes, no blinding	N	Y
6.3 Were the methods of outcome assessment comparable across intervention groups?	Outcomes were assessed using time to event data from the NCRAS data base for all patients.		Y	Not applicable
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Outcomes were assessed using time to event data from the NCRAS data base for all patients.	There may be notable errors in measurement Progression free survival (PFS). CS section 2.7.2 “progression is not recorded within the NCRAS database, time to next therapy	N	Y

		(TTNT) was used as a proxy for PFS. TTNT was defined as the time from the start of line of therapy until failure (the earliest of all-cause death or the start of a new line of treatment). Patients lost to follow-up or still in same line of treatment at the end of the study period were censored." In established literature, PFS is often defined as the time from the date of the first dose to the earlier date of assessment of disease progression or death per RECIST v1.1.		
Risk of bias judgement				
Optional: What is the predicted direction of bias due to measurement of outcomes?	There is an absence of routine data concerning progression, remission or recurrence within the cancer registry. Accordingly, there is a need to use proxy measures (e.g. TTNT for disease progression). The reliability of results from such approaches will be dependent on their validity. TTNT may overestimate the time to progression.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Low	Moderate

	TTD has been captured in the study and could be used as an alternative, lower bout, time to progression survival outcome. Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable			
Bias in selection of the reported result				
Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome *measurements* within the outcome domain?	No. Outcomes were assessed using time to event data from the NCRAS data base.		N	N
7.2 ... multiple *analyses* of the intervention-outcome relationship?	No. Outcomes were assessed using time to event data from the NCRAS data base.	Descriptive statistics. The study did not control for any confounding factors.	N	N
7.3 ... different *subgroups*?	The study captures a broad UK advanced/recurrent endometrial cancer population, with a wide range of patient characteristics. Specific subgroups within this population would have different outcomes when treated with the intervention.	The results are from a large cohort available from a national database. The results may be different if specific chemotherapies were analysed within the basket of chemotherapy or if patients had received more than one line of prior platinum doublet therapy (but having platinum doublet therapy as the last line)	Y	Y

Risk of bias judgement				
Optional: What is the predicted direction of bias due to selection of the reported result?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Moderate	Moderate
Overall bias				
Risk of bias judgement				
Optional: What is the overall predicted direction of bias for this outcome?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Moderate	Moderate

Abbreviations: EC: endometrial cancer; ECOG: Eastern Cooperative Oncology Group; N: no; NCRAS: National Cancer Registration and Analysis Service; NCRD: National Cancer Registry Dataset; NHS: National Health Service; PN: partial no; PY: partial yes; SACT: Systemic Anti-Cancer Therapy; TTD: time-to-discontinuation; TTNT: time-to-next treatment; Y: yes.

Comparison of the ERG and company quality assessments using the company's preferred tools

A comparison of ERG and company appraisal of study quality for ZoptEC and McMeekin *et al* (2015), using the Appendix C of PMG6 methodology checklist for randomised controlled trials in the old NICE guidelines manual for RCTs is provided in ERG report Appendix Table 58 and Figure 39. For ZoptEC, overall, the ERG agreed with the company on a "no" rating for 4/14 (28.6%) of items, all domains combined (selection, performance, attrition, and detection risk of bias); thus, a low or unclear risk of bias was reported for most of the domains. The ERG agreed with the company on 2/4 (50%) applicable risk of bias domains – with "low risk of bias" ratings. These domains were related to selection and performance bias. For McMeekin *et al* (2015), overall, the ERG agreed with the company on a "no" rating for 4/14 (28.6%) of items, all domains combined (selection, performance, attrition, and detection risk of bias); thus, a low or unclear risk of bias was reported for most of the domains. The ERG agreed with the company on 1/4 (25%) applicable risk of bias domains – with an "unclear risk of bias" rating. The domain was related to selection bias. The ERG and company quality assessment for ZoptEC is more comparable than that to McMeekin *et al* (2015).

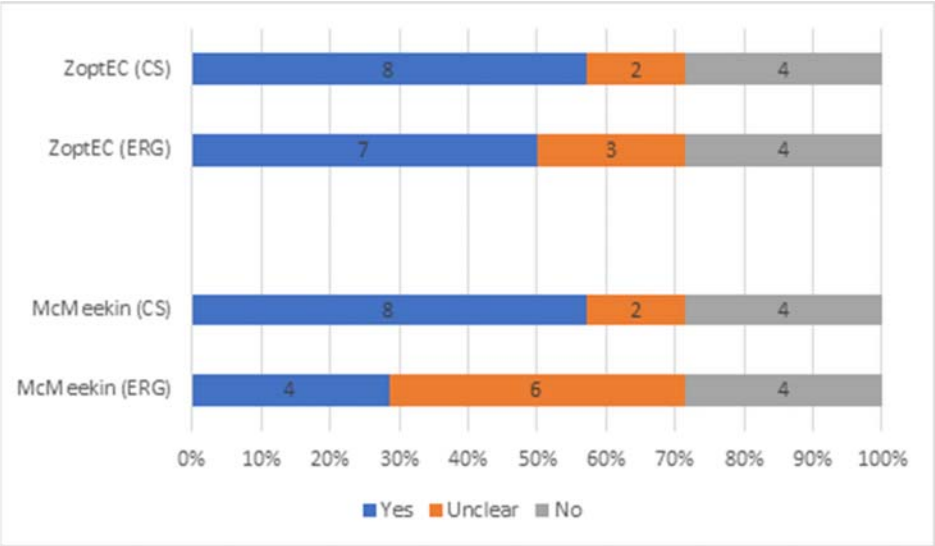


Figure 39: Comparison of ERG and company appraisal of RCTs Appendix C of PMG6 methodology checklist for randomised controlled trials in the old NICE guidelines manual

A comparison of ERG and company appraisal of study quality for GARNET, Rubinstein *et al*. (2019), Mazgani *et al*. (2008), Julius *et al*. (2013), and Makker *et al*. (2013), using the CASP check list for Non-RCTs is provided in ERG report Appendix Table 59 and Figure 40. A 'no' rating on the checklist was reported as a high risk of bias, and a 'yes' was reported as a low risk of bias. There were differences between the ERG and company judgements for overall risk of bias in most of the studies, except Julius *et al*. (2013). The ERG noted an overall moderate risk of bias, while the company noted a low risk of bias for the GARNET trial. For Rubinstein *et al*. (2019), Mazgani *et al*. (2008), and Makker *et al*. (2013), the ERG noted an overall moderate risk of bias, while the company noted a high risk of bias. For Julius *et al*. (2013), the ERG agrees with the company's judgment of an overall high risk of bias.

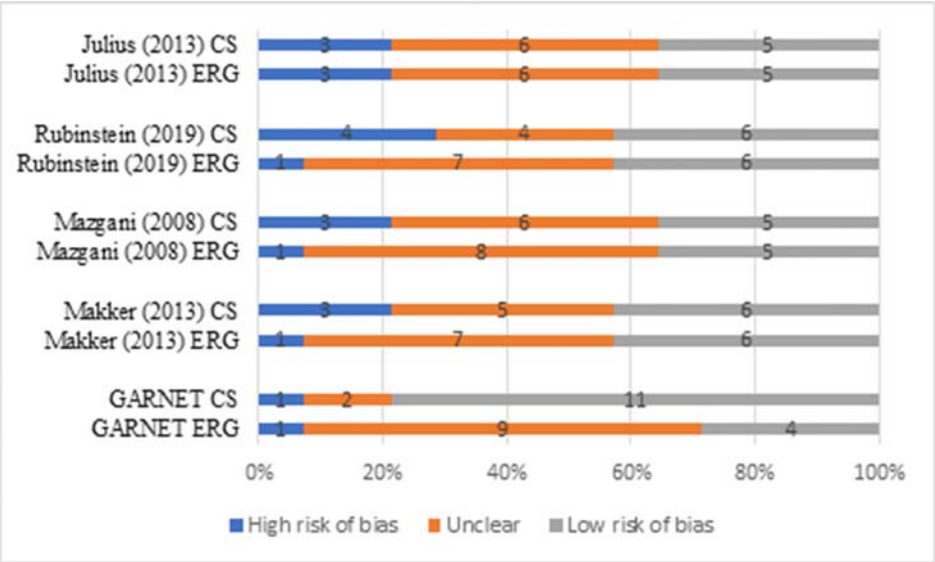


Figure 40: Comparison of ERG and company appraisal of Non-RCTs using the CASP check list

A comparison of ERG and company appraisal of the study quality for the UK RWE study, using the ROBINS I assessment tool is provided in ERG report Appendix Table 60 and Figure 41. The ROBINS I tool evaluates the risk of bias using seven domains (including: confounding, participants selection, the classification of intervention, deviation of intervention, missing data, outcome measurements, and bias in the selection of the reported results). Concerning the bias due to the confounding, participants selection, the classification of intervention, missing data, and bias in the selection of the reported results, the ERG agrees with the company's judgments. For bias due to deviations from intended interventions, the ERG and the company's judgements differ on all items. The ERG notes that there was insufficient information on the administration of the basket of therapies. It is therefore unknown if any deviations would lead to bias in the effect estimate. For bias due to measurement of outcomes, there was a difference in 3/4 (75%) of the items. The ERG agrees with the company with an overall "moderate risk of bias".

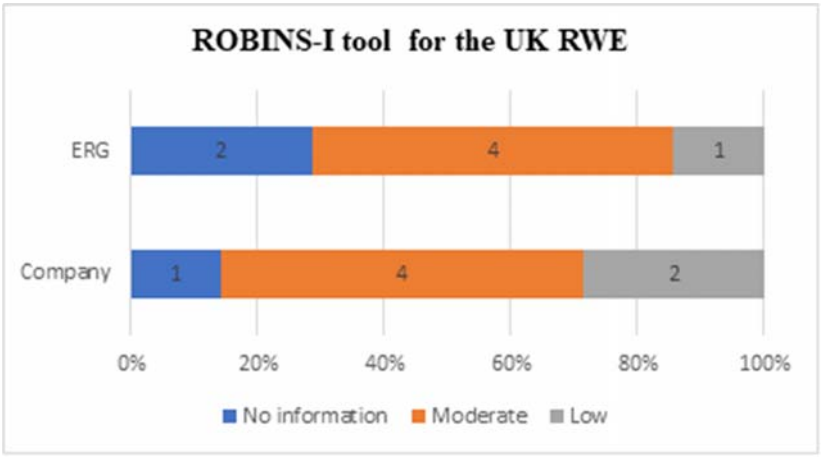


Figure 41: Comparison of ERG and company appraisal of included studies using the ROBINS I assessment tool for the UK RWE study

ERG quality assessments using the NICE preferred tools

For the more applicable Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) checklist, the overall risk of bias for studies with low risk of bias in all domains was judged as "low risk of bias", while some concerns in multiple domains or a high risk of bias in at least one domain was judged as "high risk of bias". Both the ZoptEC trial and McMeekin *et al* (2015) study had an overall judgment of "high risk of bias". A summary of results is presented in Figure 42.

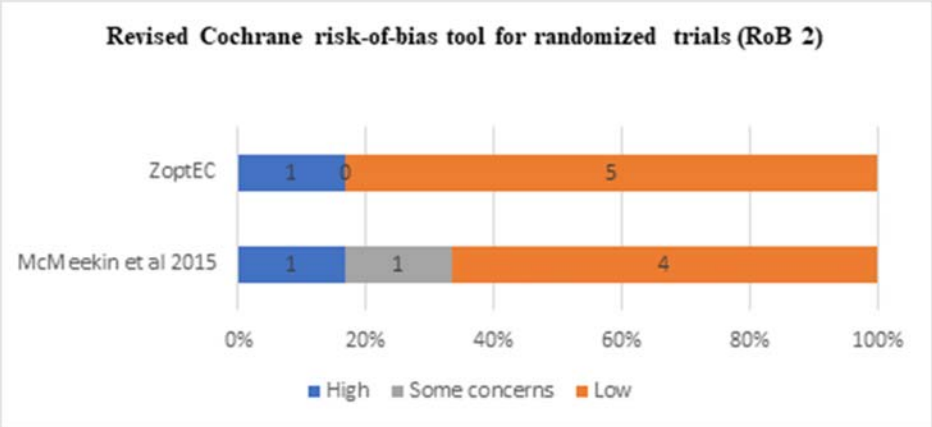


Figure 42: ERG appraisal of included studies using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) Appraisal checklist

For the Institute of Health Economics Quality Appraisal Checklist for Non-RCTs, a 'no' rating on the checklist was reported as a high risk of bias, and a 'yes' was reported as a low risk of bias. A summary of results is presented in Figure 43. Most of the studies had

low or partial risks of bias. The ERG considers the GARNET trial of better quality than the primary comparator evidence (UK RWE study), GARNET had about 90% of the items rated as low or partial/unclear risks of bias, while the UK RWE study had about 65% of the items rated as low or partial/unclear risks of bias.

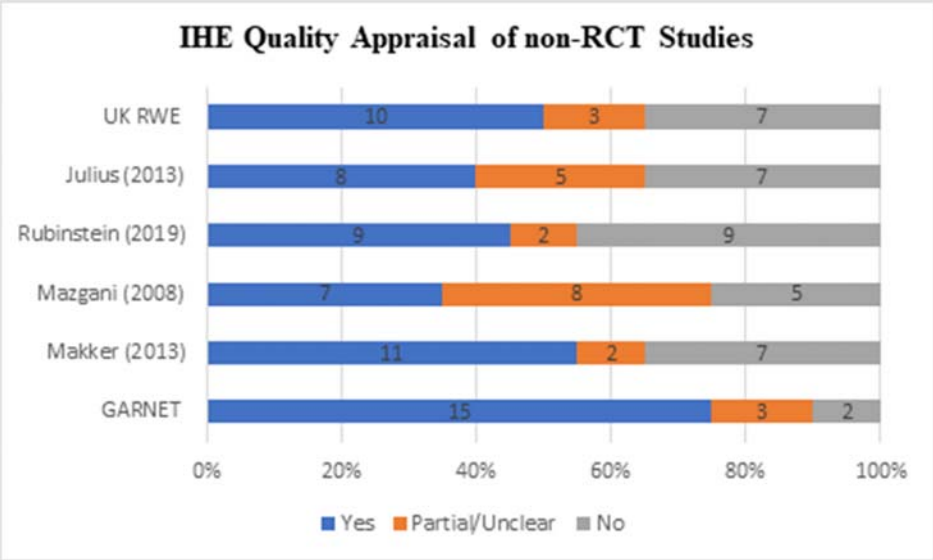
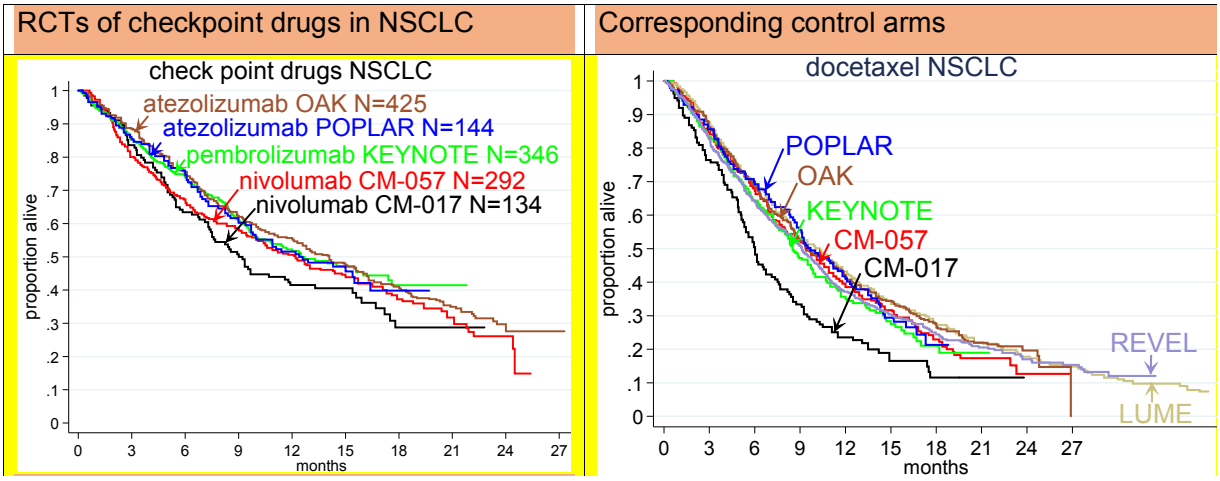


Figure 43: ERG appraisal of included studies using the IHE Quality Appraisal Checklist

9.2 *Trajectories of KM OS curves from trials of checkpoint inhibitors for treating non-small cell lung cancer (NLSCLC)*

The ERG looked at the trajectory of KM OS plots in RCTs of checkpoint drugs in non-small cell lung cancer (NLSCLC).[34-36] The trajectories exhibit a gradually decreasing slope without the pronounced long flat tail seen in the GARNET single arm study; a similar trajectory is seen in the large recent gastro-oesophageal cancer CHECKMATE 649 RCT[37] and in the NICE STA ID 1019 for pembrolizumab in previously treated advanced / metastatic urethral cancer (based on a single arm study). The control arms in such RCTs show a similar trajectories. The ERG consider it likely the pronounced flat tail in GARNET is contributed by small patients numbers and immature follow up more than by extended treatment effects.



CM=CheckMate

Figure 44: Trajectory of KM plots for patients in trials of checkpoint inhibitors for non-small cell lung cancer (NSCLC)

9.3 *ERG critique of company's approaches to OS and PFS modelling with extrapolation to 40 years*

The company's approach, described on CS page 137, entailed the following elements:

- Assessment of proportional hazard assumption (dostarlimab vs. RWE)
- Use of information criteria to judge goodness of fit of parametric models
- Visual inspection of extrapolated parametric curves versus observed KM curves
- Clinical plausibility of short and long term survival estimates based on discussion with and survey of UK clinical experts opinions

The observed OS and PFS KM plots for dostarlimab (GARNET: CS Figures 11 and 13) are characterised by changes in trajectory of the curve (especially for OS) and long flat tails from about 18 months to 32 months during which few patients were at risk and there was a sparsity of events (Xxxxxxx45). Most parametric models are unlikely to fit well to changing trajectory in the observed data and for some models the flat tail is likely to strongly weight extrapolations extending to 40 years (Xxxxxxx45). These features may be contingent on the small number (N=129) and possible heterogeneity of patients and immaturity of observation.

9.3.1 OS dostarlimab (GARNET)

The company rejected the assumption of proportional hazards and explored a complement of nine parametric models extrapolated to 40 years. The ERG has reservations about the extended time horizon and the potential influence on modelling of the flat tail in the KM data. On extrapolated to 40 years the CS parametric models other than exponential, Weibull, and gamma provided implausibly generous survival predictions with significant survivors well beyond 40 years (Xxxxxxx46). It can be noted that at 5 years the ggamma model generates easily the best survival of eight models other than the nearest rival (Gompertz model) that predicts about 40% patients as immortal.

45

[redacted] 46 [redacted]

On the basis AIC/BIC scores (CS Table 55) the company selected the ggamma model as best fit. This model generates clearly implausible >20% survivors after 40 years and about 18% after 55 years. The CS justifies the choice of the ggamma model by pointing to the correspondence between the treatment-waning adjusted ggamma model and the mean of seven expert clinicians' opinions about survival at 3, 5, 10,15 and 20 years; to the ERG this seems to be a teleological construction. The ERG consider that a more plausible parametric model would be better selected before any waning adjustment is applied, and point out that the mean of seven clinicians' predictions ignores the range inherent in clinicians' opinions and also the uncertainty associated with the estimation of a proportion. The ERG think that for an average clinician value to be useful a survey involving a larger number of experts may be required. Xxxxxxx47 summarises the individual clinician predictions at 3, 5, 10, 15 and 20 years (based on CS Table 56); these are predicted proportions for 129 patients and the ERG have attached binomial 95% CIs. Considerable variation is evident. It is unclear to the ERG if clinicians were appraised or not appraised of the possibility of waning when making their estimates. As an approximation of full variation associated with the predictions the ERG takes the range from the lowest 95% CI to the highest 95% CI at each of the years predicted. These ranges are represented as vertical bars in Xxxxxxx46 (for unadjusted OS) and in Xxxxxxx48 (for waning-adjusted OS).

Xxxxxxx46 indicates that all models (unadjusted for treatment-waning effect) are encompassed within clinicians' range of predictions (the only exception being the Gompertz model at 20 years). Xxxxxxx48 indicates that this is still the case at most years after waning adjustment of most models. The ERG suggest that the clinical predictions may be associated with too much uncertainty to strongly support any particular choice of parametric model.

47

[redacted]

The company's treatment waning-adjusted ggamma model predicts an implausible 4% survivors at 40 years; however in the CS economic model this treatment-waning adjusted ggamma model is further adjusted by "capping" from 20 to 40 years so that survival does not exceed that for a matched UK general population. That capping is required from 20 years onward implies a time horizon of 40 years might be too extended. Two STAs of PD1 drugs quoted by the company employ shorter time horizons of 20 years[38] and 25 years;[39] a 40 year horizon was used in TA578,[40] but sensitivity analysis with shorter time horizons increased the ICER substantially. At 20 years the waning adjusted ggamma model suggests about [redacted] of patients are cured of endometrial cancer and will suffer the same mortality from other causes (other cancers, heart disease etc) as the matched general population.

9.3.1.1 Influence upon parametric models of the flat tail in the observed data

Some of the CS parametric models extrapolation to 40 years may be sensitive to the flat tail seen in the KM plots. To monitor this potential influence, particularly in regard to the CS-selected ggamma model, the ERG split the KM plot at various time points so as to reduce the size of the flat tail; the "reduced data" was then modelled using standard parametric models. The data was split at 14.6, 18.5 and 20.64 months and compared with models using the complete KM plot (no split). The results (Xxxxxxx49) indicate that the Gompertz and ggamma models are sensitive to the extent of the flat tail and at each split time the ggamma models generate implausible proportions of survivors when extrapolated to 40 years.

49

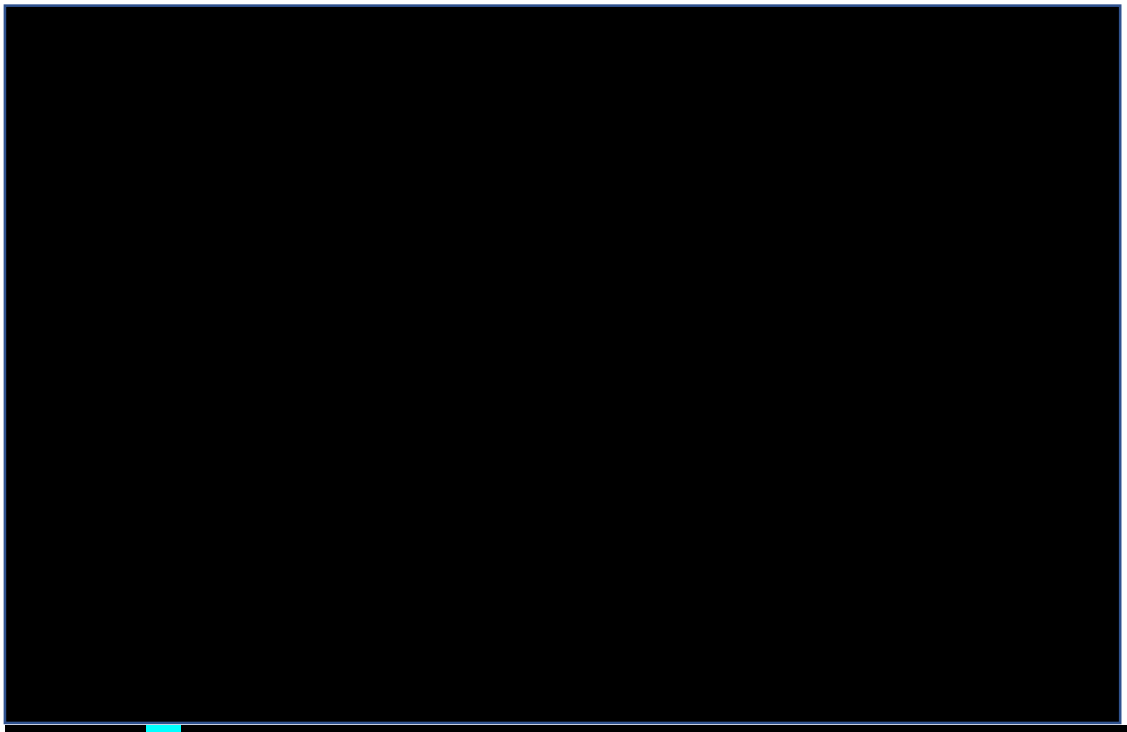
9.3.1.2 Adjustment for treatment waning

The company's justification for applying treatment-waning is stated as follows: "*treatment waning assumptions were applied in line with UK clinical expert feedback and previous appraisals of I-O therapies*" (CS section B.3.3.4; page 137). Information supplied in clarification identified one of the questions to be posed for clinical experts as "[redacted]?" The ERG have been unable to identify the clinicians' quantitative responses among clinical responses supplied in clarification.

In the company base case waning adjustment the unadjusted ggamma model was used for the phase 0 to [redacted], the phase from [redacted] to 40 years was fully waning-adjusted so that "*efficacy associated with dostarlimab was assumed to be equal to the efficacy associated with current clinical management*", this was achieved by applying the MAIC HR of 0.35 (95% CIs: 0.22 - 0.55; CS Table 24) from [redacted] onward; for

the phase between [redacted] the waning effect gradually changed from zero to full waning (a linear change in hazard).

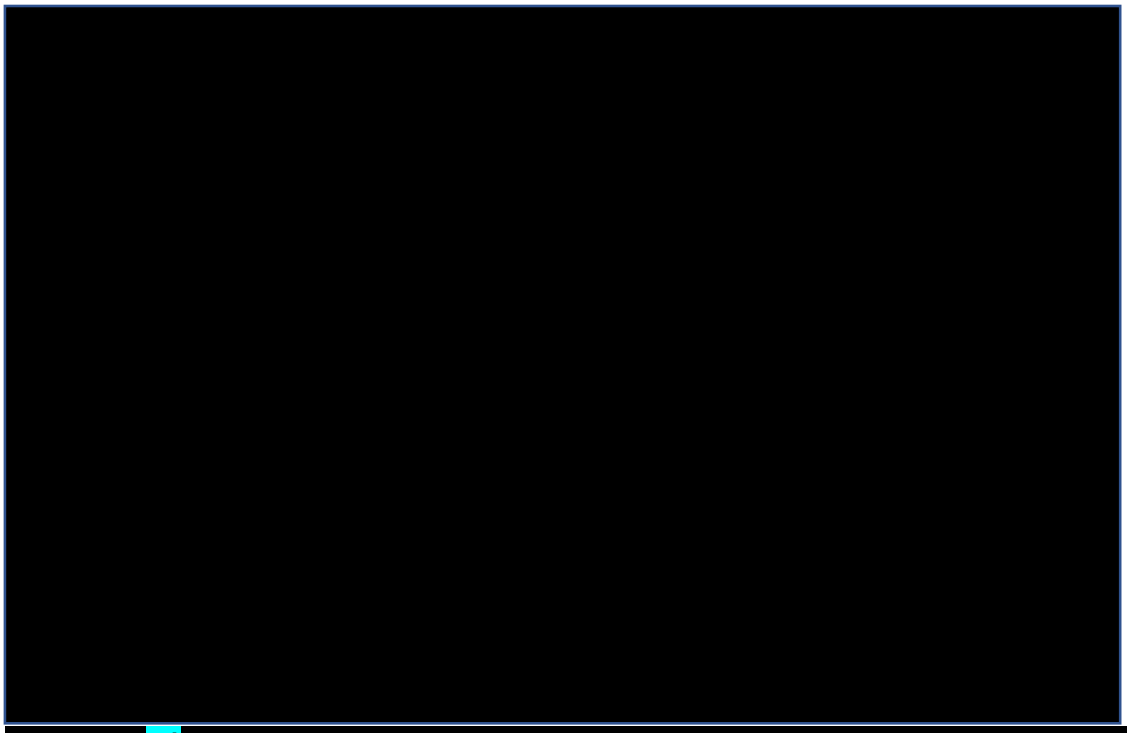
[redacted]50 shows the hazards (left) and OS (right) for the company's treatment-waning adjusted and unadjusted ggamma models.



[redacted]50

Xxxxxxx50 right shows that the company's waning adjustment exerts a large influence on ggamma modelled OS, reducing the predicted proportion alive at 40 years from >20% to ~ 4%. Using alternative HR values (from within the MAIC 95% CIs) of 0.25 and 0.5 (rather than 0.35) indicates considerable sensitivity of the ggamma model to the HR applied. Even with HR of 0.25 there remain predicted survivors beyond 40 years.

Corresponding results for the company's exponential and Weibull models are summarised in Xxxxxxx51 and Xxxxxxx52 (see Appendix 9.6 for waning-adjusted hazards for all CS models). The influence of waning on exponential and Weibull modelled OS seems muted relative to that seen for the ggamma model.



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The company's unadjusted spline models generate survivors beyond 40 years but with waning adjustment survivors at 20 years are reduced to <1% producing curves very similar to the unadjusted exponential and Weibull models. Loglogistic and lognormal models do not support proportional hazards and using the MAIC HR to for these models does not seem appropriate.

The ERG consider unadjusted and adjusted exponential and Weibull models and possibly waning adjusted spline models represent more plausible extrapolated survival than the company's unadjusted or waning-adjusted ggamma models.

Table 61 summarises ERG comments regarding the steps taken by the company to justify its selection of the waning-adjusted ggamma model.

Table 61: Summary of company's selection procedure for waning-adjusted ggamma model of dostarlimab OS

Step	Company's modelling	ERG Comment 1	ERG Comment 2
1	Make selection of preferred model by comparing extrapolated models with the mean of clinicians' predictions of survival (at 3, 5,10,15, 20 years)	The mean of clinicians' predictions fails to reflect the wide variation between predictions of individual clinicians; when this variation is accounted for all models fall within range of clinicians' predictions.	The clinicians' predictions are too various to strongly indicate superiority of any model over an alternative. A survey of opinions of a larger number of experts would seem desirable.
2	Select ggamma model on basis that the waning-adjusted ggamma model conforms to the mean of clinicians' predictions	This seems teleological (selection to serve purpose). The selected model should conform to the mean of clinicians' predictions before waning-adjustment as well as after. The ggamma model requires treatment waning adjustment to conform to the mean of clinicians' predictions, but still generates implausible survivors at 40 years.	Only exponential Weibull and gamma models generate reasonable extrapolation without waning adjustment; other models predict survivors beyond 40 years. The unadjusted ggamma model generates very implausible extrapolation (>20% alive at 40 years). The waning-adjusted ggamma model generates more modestly implausible extrapolation (>4% survivors at 40 years).
3	The gamma model has reasonable AIC/BIC scores (rank1 on AIC; rank 3 on BIC)	The differences between models in IC score is fairly trivial for a KM curve with multiple changes in trajectory.	AIC/BIC scores can be influenced strongly by the long flat tail in the observed KM plot. This is seen particularly with CS Gompertz and ggamma models
4	The waning-adjusted ggamma model requires capping so that survival rate does not exceed that of the matched general population.	For the waning-adjusted ggamma model capping was required from year 20 to year 40.	The capping requirement implies that the waning-adjusted ggamma model may be over-generous in survivors upon extrapolation and that a time horizon of say 20 or 25 year used in other PD1 STAs may be appropriate.

9.3.1.3 OS Conclusion/summary

The company's parametric models either fit poorly to the observed data (according AIC/BIC scores and or visual inspection) or predict implausible survival in extrapolation with decreasing hazard to 40 years that seems inconsistent with an ageing population, likely due to the influence of the long flat tail in the observed data. The company considers that "*the extended tail of the KM curves (that) is the hallmark of I-O therapies" , and point out that "in other cancers, I-O therapies have been shown to result in extended treatment benefits and long-term remission even after treatment discontinuation, offering a substantially improved prognosis for many patients.* [41] *Indeed, the long-term benefits of I-O therapies have been demonstrated across multiple indications including melanoma, lung, head and neck, where patients who discontinued therapy had durable responses that extended beyond the end of treatment.* [42] *Given this trend, it is reasonable to believe some patients who respond to dostarlimab may continue to experience extended treatment benefits and long-term remission beyond the two-year follow-up in the GARNET trial to date*".

Summary of time to event evidence from GARNET

The single arm phase 2 GSK study GARNET provided time to event analysis evidence in the form of Kaplan Meier plots about overall survival, progression free survival and time on treatment for 129 patients treated with dostarlimab with maximum follow up of ~30 months. To varying degrees the plots exhibit multiple changes in trajectory and long flat tails where few events occur and few patients are at risk. The company's position is that the plots are typical of PD inhibitors and that they indicate particularly long term benefit in a sub population of good-responders. The ERG position is that these characteristics may depend on a too small and heterogeneous population being followed up for too short a time in the absence of a comparator. The company's position might be supported if these KM characteristics were uniquely and universally found for this class of drug in both endometrial and other cancers but were not seen with alternative therapies for endometrial cancer. The company has not presented data that support their position other than a few references and an interpretation of clinicians' opinions. The ERG has done a rapid analysis of some available relevant studies.

Further modelling in company submission

The company explored the use of observed KM data until the flat tail was reached, followed by parametric modelling thereafter. Unsurprisingly this modelling resulted in very unrealistic extrapolations due to the lack of events and flatness in the tail of the observed data, and was rejected by the company.

The ERG have explored the influence of the flat tail on extrapolation of parametric models by splitting the observed data at several time points in the flat tail and extrapolating thereby to generate models that encompass reduced influence of the flat tail (see Appendix section 9.3.1.1).

9.3.2 PFS dostarlimab (GARNET)

The company used the same procedures as for OS. Treatment waning was applied to parametric models of PFS; the ERG have not previously encountered such application to PFS and are unsure of the company's justification for doing so. The KM plot has an even more extensive flat tail than seen for OS; consequently no parametric models fit the KM well. Models with superior AIC/BIC aggregate scores generate extrapolations predicting that after about 14 months many un-progressed patients ([redacted]) will remain without progression to 40 years.

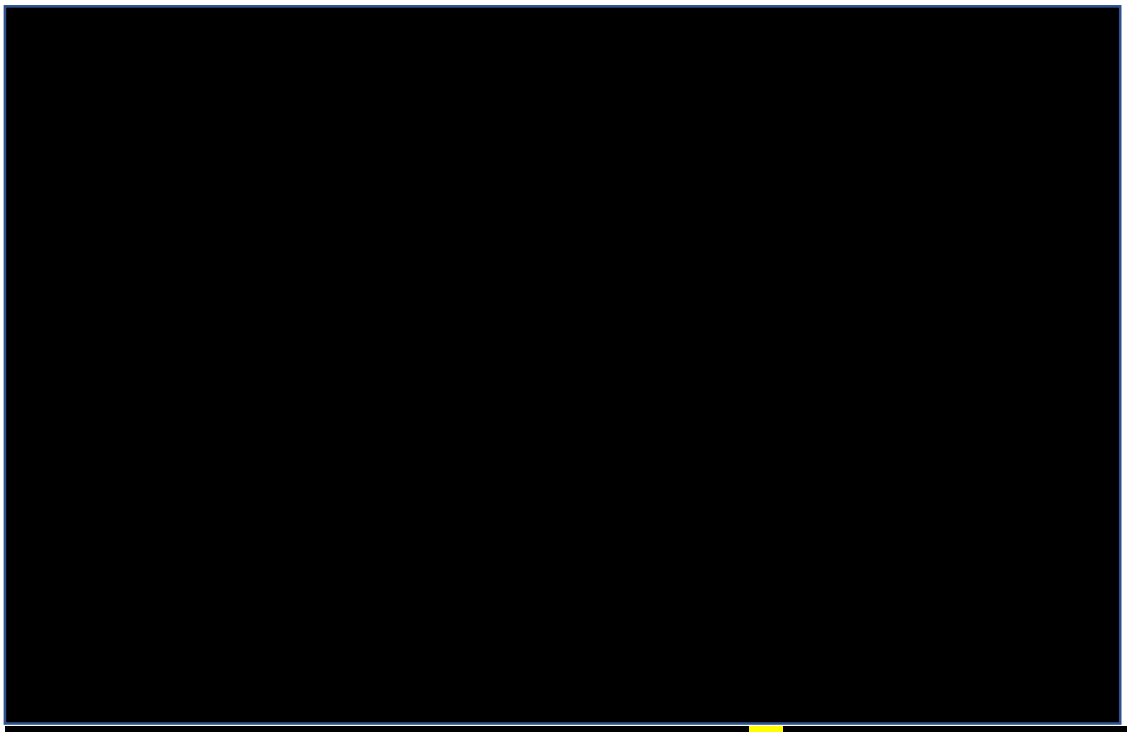
According to AIC/BIC values (CS Document B Table 50) the best ranking parametric fits were supplied by spline, ggamma and Gompertz models; however with or without application of treatment waning these generate unrealistic extrapolations to 40 years and were rejected by the company. As base case model the company selected the lognormal model. This generated more plausible extrapolation to 40 years but provided a poor fit to the PFS KM (CS Document B Figure 41) and tallied poorly with clinicians' predictions (Xxxxxxx53 and xxxxxx54). In choosing the lognormal model the company disregard the clinicians' PFS predictions stating "*however, based on plausibility considering the OS extrapolations, a more conservative survival curve, the lognormal, was identified for use in the base case*". The ERG find this teleological and do not consider this a sound argument since the plausibility of the company's ggamma model

for OS is far from obvious (see section above). The impact of selecting the lognormal model for PFS in conjunction with the ggamma model for OS is to greatly promote the accrual of post-progression survival benefit even though dostarlimab treatment has long ceased (see following section).

The PFS predictions of seven clinical experts were far less variable than for OS (Xxxxxxx55), with one respondent tending to be an outlier that influences mean values. The outlier predictions at 15 and 20 years are very different to those of the other six clinicians. ERG assessment of the variation in clinicians' predictions has discounted the outlier and, as for OS, has taken the range from lowest to highest 95% CI. These are plotted as vertical bars in Xxxxxxx53 and xxxxxx54.

The mean and range of clinicians' predictions seem somewhat unrealistic in that patients remain without progression after 15 to 20 years even though clinical opinion is that treatment would cease after [redacted]. The CS is inconsistent in the use and weight given to clinicians' predictions, accepting those for OS but rejecting those for PFS. As stated above and elsewhere the ERG find clinicians' predictions are associated with too much uncertainty to be used as a sound guide for modelling.

Because of the influence of the accentuated flat tail of the PFS KM plot and the seemingly optimistic clinicians' predictions of progression it is difficult to select a suitable parametric model and to decide if treatment waning represents a valid adjustment. The ERG explored additional models that might fit clinicians' predictions more consistently than seen in the CS. In particular bathtub and Rayleigh models of OS and PFS failed to generate superior models to those generated by the company.



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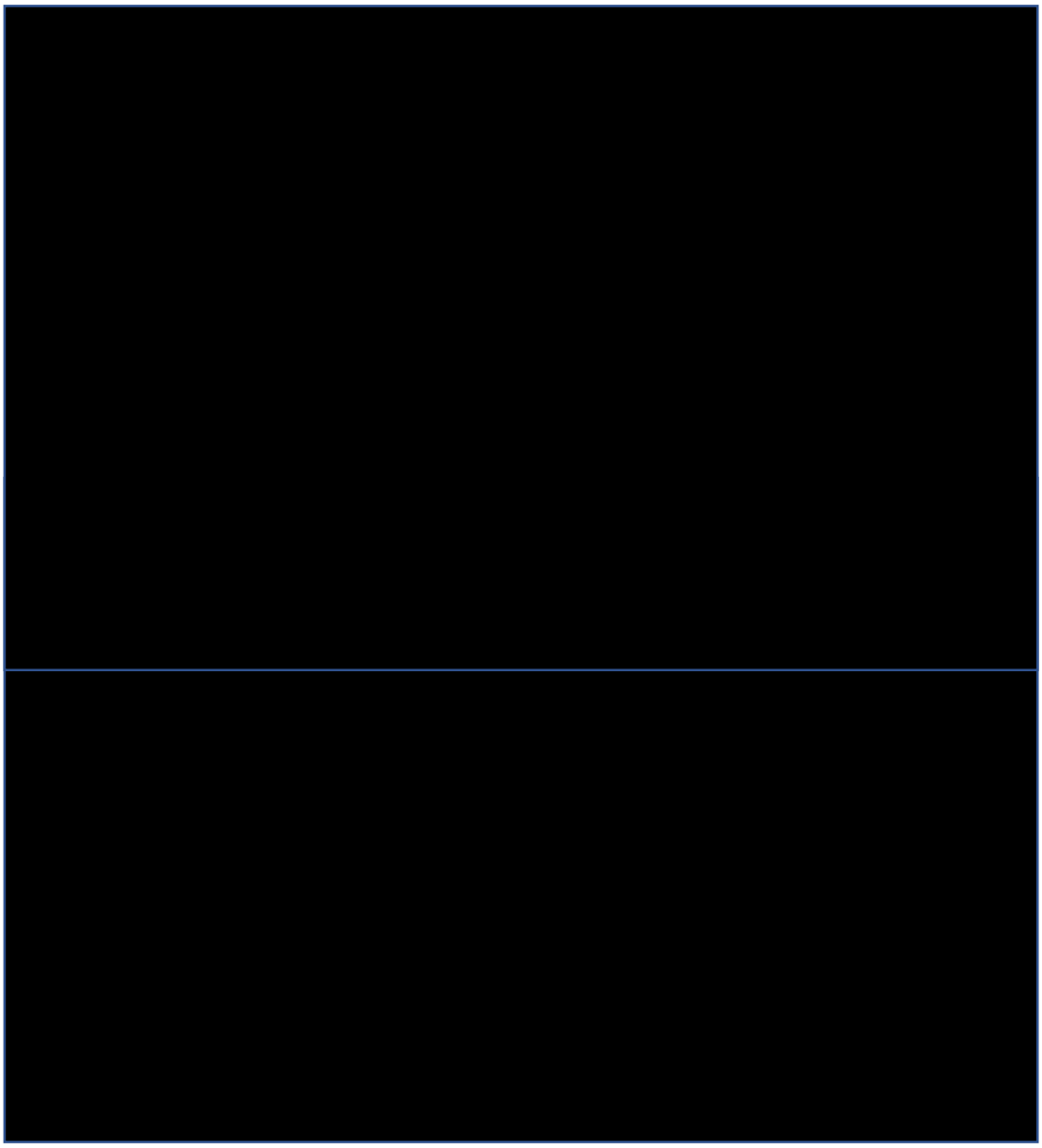

9.3.2.1 Impact of CS selection ggamma and lognormal models for OS and PFS

Modelling PFS and OS partitions LY and QALY accrual between pre-progression benefit (estimated from the area under the PFS curve) and post-progression benefit (estimated from the area between OS and PFS curves). When time on treatment ([redacted]) is short compared to the modelled time horizon (40 years) accrual of pre-progression benefit is generally expected to be greater than that for post-progression benefit since any treatment effect will terminate and / or wane relatively early.

Xxxxxxx56 shows the accrual of LY benefit in pre-progression and post-progression during the KM phase of ~32 months (left) and during the CS models extrapolated to 20 years (right) and compared to expert clinicians' mean estimates. During the KM phase pre-progression gain (brown) is much larger than post-progression gain (green), whereas after extrapolation using the company's models of OS and PFS the reverse is the case (pale green area is much greater than pale brown area). Further extrapolation beyond twenty years (240 months) perpetuates this trend. This result is reflected in the output of the company's economic model where 61% of total life years for dostarlimab accrues in post-progression. In contrast to this the mean of clinician's predictions for OS and PFS implies that on average the clinician's do not think there would be post-progression gain after 120 months. The company base case selection of model for OS seems overgenerous relative to clinicians' opinion while in contrast the base case model for PFS greatly underestimates PFS relative to clinicians' opinion. This results from the company's inconsistent use of clinical opinion (see above).

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9.4 *ERG alternative modelling of OS and PFS*

For reasons explained in previous sections the ERG think the base case models proposed by the company are likely inappropriate.

9.4.1 GARNET

The relatively small number of patients (N=129) in GARNET and the single arm nature of the GARNET study, together with the changes in the trajectory of the KM plot for OS, and the pronounced flat tails seen in both the KM plots for OS and PFS, means that any modelling for extrapolation will unavoidably be associated with considerable imprecision; this will also apply for the results of the MAIC analyses, that were undertaken by the company as supporting evidence, and in which the dostarlimab sample size was further reduced.

The ERG therefore explored several alternative modelling options that seem more appropriate in extrapolation than those selected by the company. In particular OS was

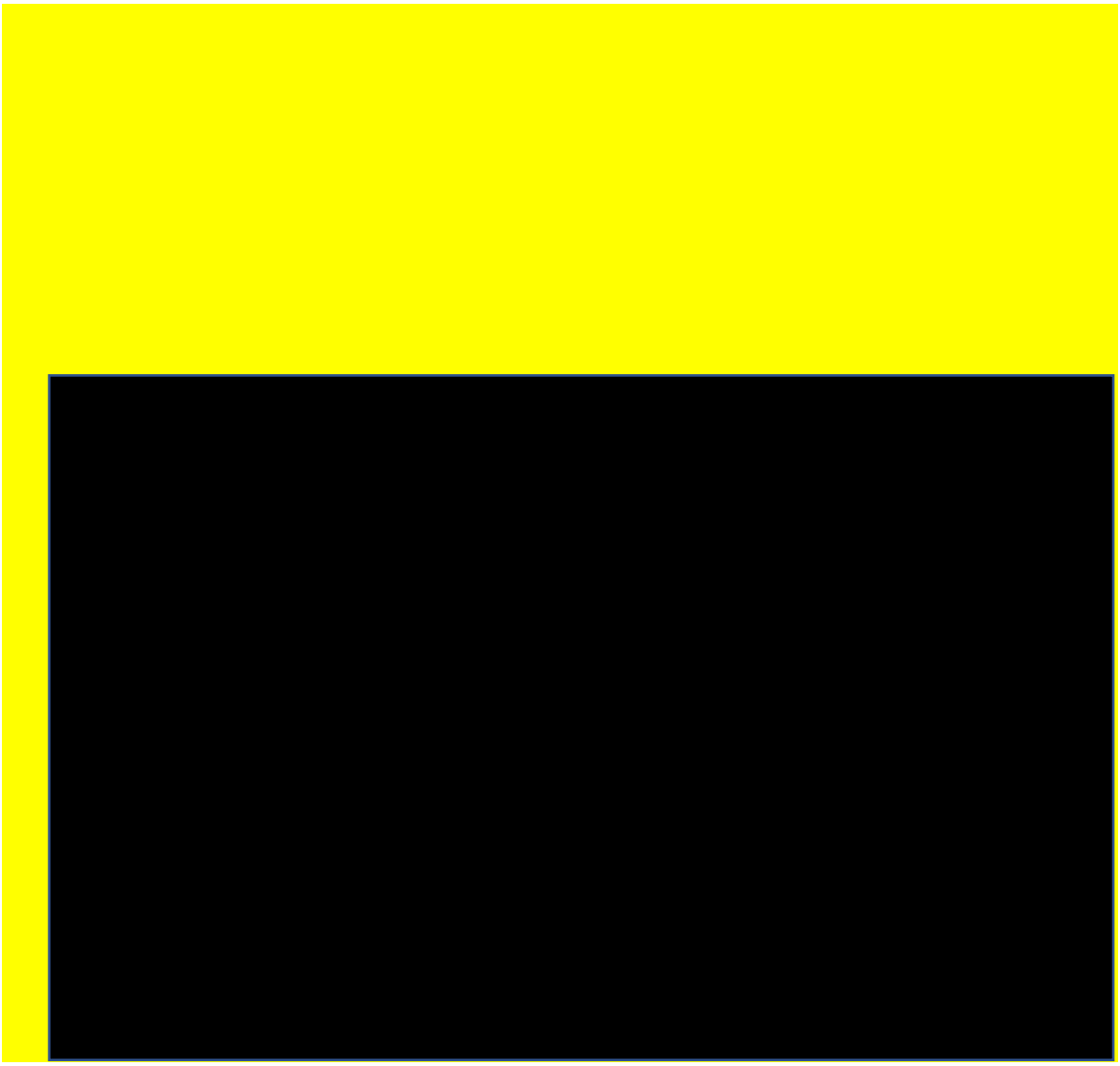
modelled with the treatment waning-adjusted Weibull distribution rather than the company's over-generous waning adjusted ggamma model, and PFS by adjusted and unadjusted Weibull models rather than the company's lognormal model. The results are summarised in Xxxxxxx57.

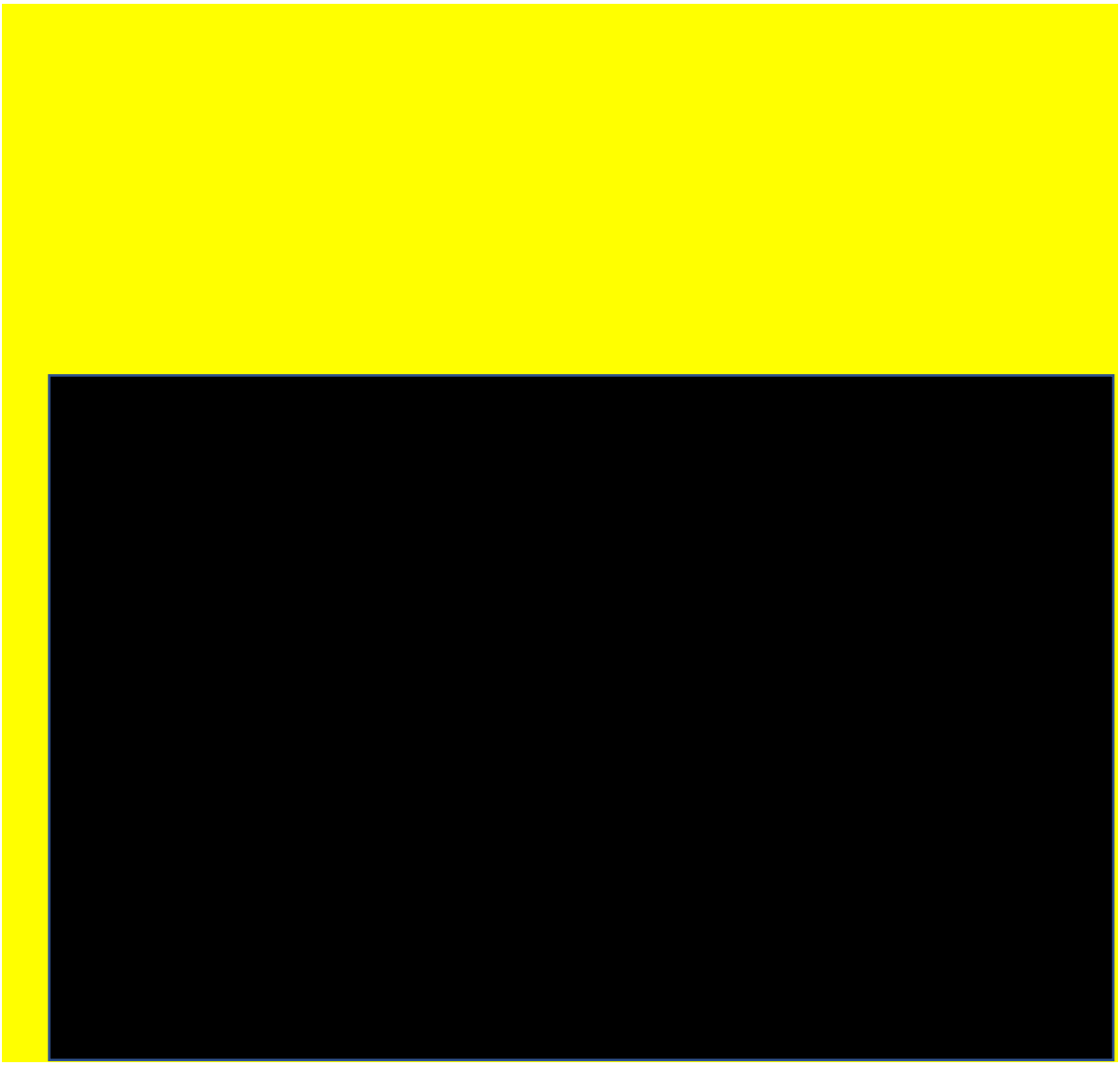
With the ERG models the area under the curve (AUC) estimates of pre-progression survival benefit accrual is greater than that for post-progression benefit. The unadjusted Weibull model for PFS requires capping to equal OS at a late stage of extrapolation so as to avoid predicting progression of dead patients. The adjusted PFS curve does not encounter this problem.

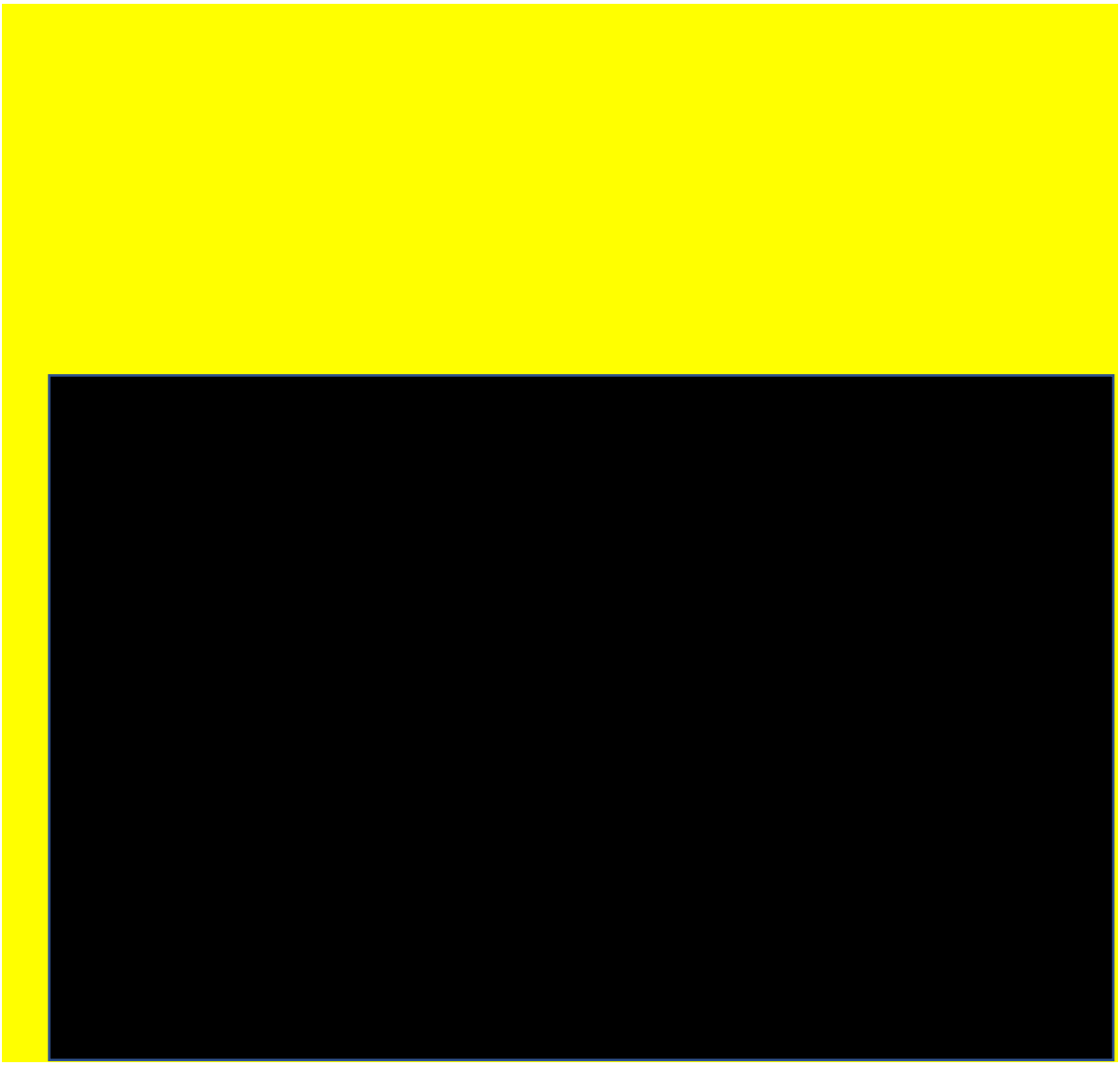
9.4.2 RWEQ

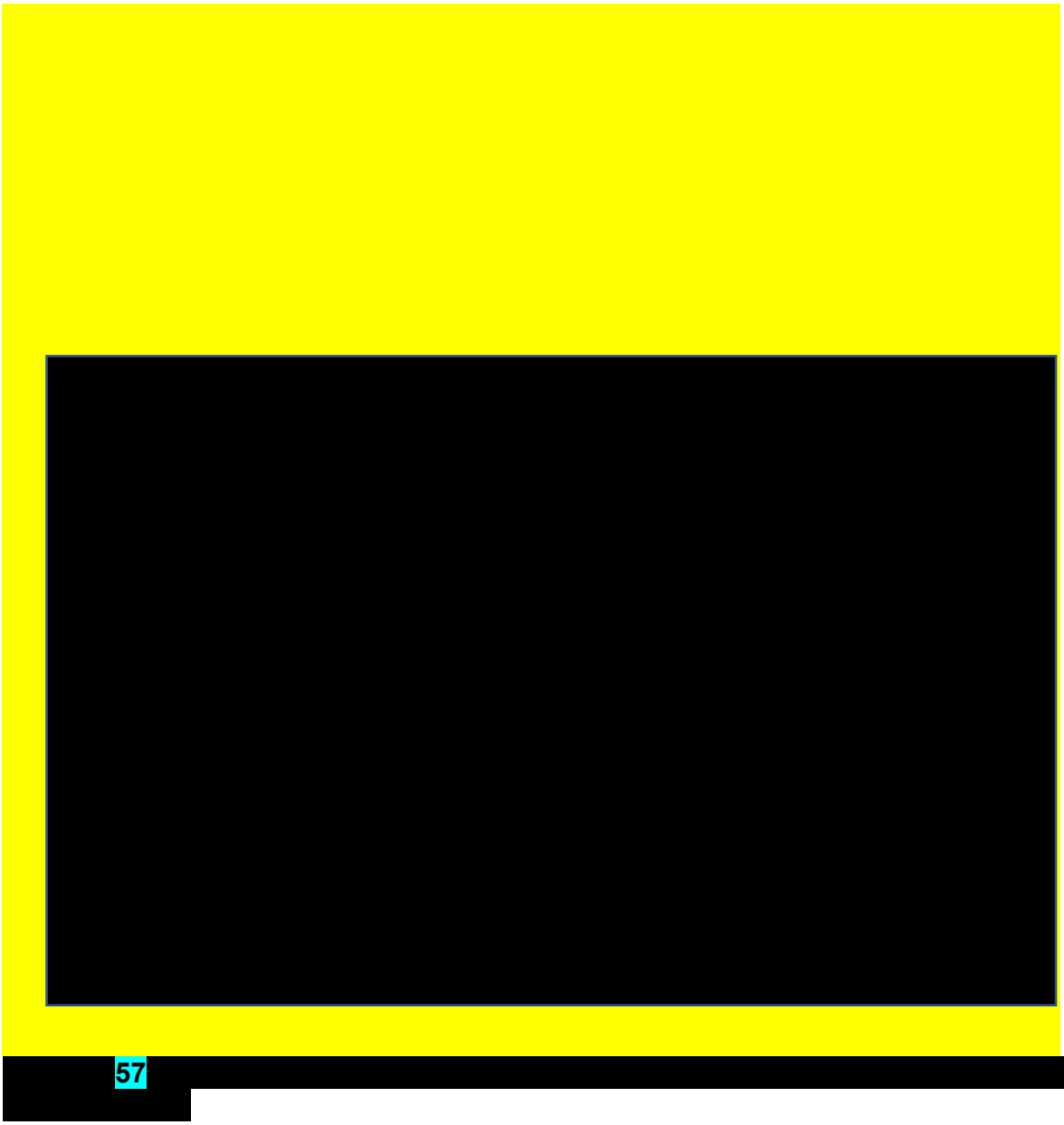
In contrast to the GARNET study the RWE KM data for PFS and for OS was mature (survival less than 15% at end of follow up), exhibited internally consistent trajectory, and was based on a large number of participants (N=[redacted]).

Xxxxxxx58 summarises observed OS and PFS (KM plots), the company's selected loglogistic (OS) and lognormal (PFS) models and clinicians' predicted PFS and OS at 5, 10, 15, and 20 years. The area under the curves allows estimation of accrual of observed pre-progression and post-progression LYs benefit. Model fit to KM OS and PFS is good, and clinicians' predictions, although slightly optimistic align well with both observed and modelled results. Gained LYs are more balance between pre-progression and post-progression than seen with the company's models for the population receiving dostarlimab. The ERG note that a model that more closely matches the clinicians' predictions would be more consistent with the company's position of clinician-led modelling.









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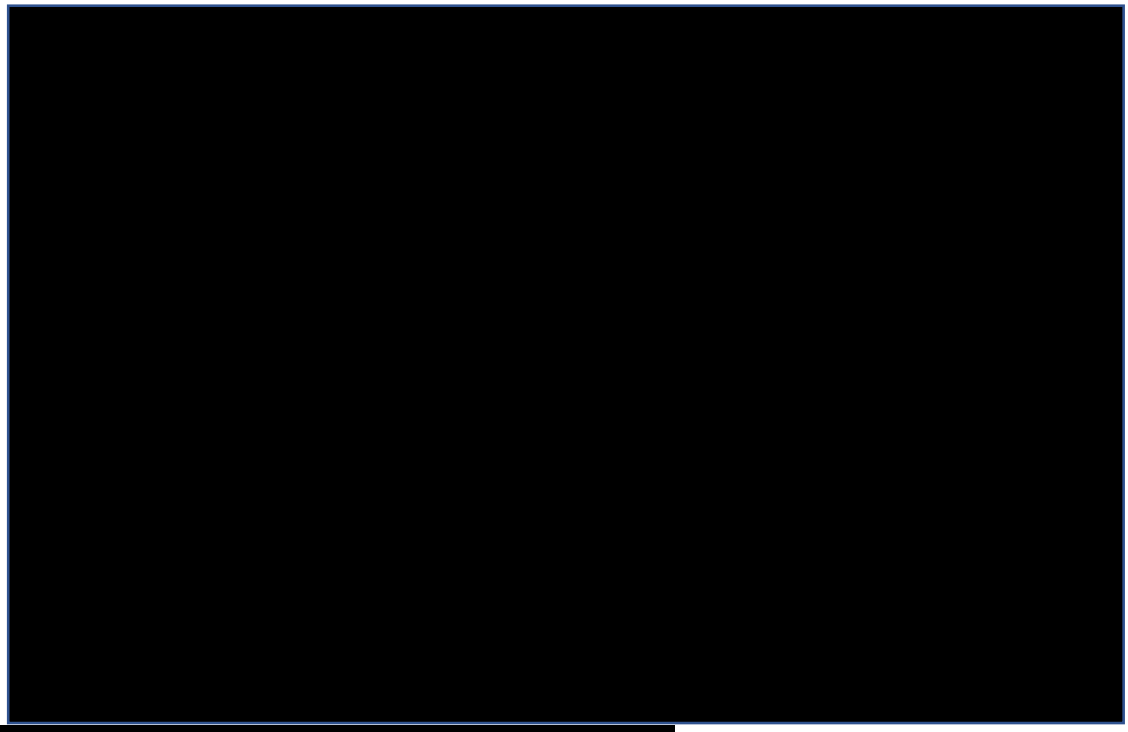
[redacted]58[redacted]



[redacted]

The ERG therefore explored additional models using IPD developed from the KM details supplied by the company in clarification. A cubic spline model with 3 knots generated superior AIC values than loglogistic and in extrapolation more closely aligned with the clinicians' predictions than did the company's loglogistic model (Figure 59) but eventually flattens dramatically and seems less suitable than the CS loglog model.

Figure 59: RWEQ KM, loglogistic, and cubic spline models, compared to clinicians' predictions

9.5 *GARNET data on time on treatment with dostarlimab*

The company's model of time on dostarlimab treatment involved the following stages: [i] parametric models were fit to the observed KM plot for ToT; [ii] selection of the loglogistic model from among candidate parametric models (CS Figure 53); [iii] operation of the loglogistic model for [redacted] at which time point the proportion of patients continuing treatment was reduced to [redacted] of the starting population; [iv] continuation of the loglogistic model from [redacted] to [redacted] (reducing the proportion in treatment from [redacted] to about [redacted]); [v] discontinuation of treatment at [redacted]. The resulting model is shown in CS Figure 54. The justifications for this model were expert clinical opinion sought by GSK during a consultancy exercise said to support the [redacted] changes in the loglogistic model, the fact that this procedure had been

judged appropriate in the NICE appraisal of an analogous I-O therapy (avelumab) for Merkel cell carcinoma, and the appropriateness of the loglogistic model.

The ERG's critique of the company model includes the following points: the ERG found that the company model used the efficacy ToT KM but referred to this as ITT; since the observed data is only referenced for the first 2 years the ERG believe the parametric fit selected should be that which best fits the 0 to 2 year observed data; the amongst the clarification material supplied about the GSK clinical expert consultation the ERG failed to find supporting quantitative clinical expert opinion regarding the [redacted] cuts or the reduction to [redacted] introduced at [redacted]; the ToT model accepted by the avelumab appraisal committee included a 2 year reduction to 33% in treatment rather than to [redacted] These points are explained in more detail in the following section.

The company modelled treatment arms separately and stated (CS section B.3.3.7) "*standard parametric distributions described in CS Section B.3.3.3 were fitted to the ToT data for the ITT population (N=129) in GARNET to estimate ToT for dostarlimab within the model*". The modelled ToT KM plot exhibits several changes in trajectory and a long flat tail. In clarification the ERG received underlying data for ToT in the ITT population. This indicated that the first events occurred in [redacted] patients at [redacted] months (reproduced in Xxxxxx62).

[redacted] **62** [redacted]

Day	Month	Event	Censor	N at risk	S(t)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

This yields the KM plot shown left in Xxxxxxx60. However in the company economic model the ToT KM plot is for the efficacy population (N=[redacted]), the corresponding KM plot is shown in [redacted]60 right in which multiple events occur early at [redacted] months rather than [redacted] months; this plot corresponds to the KM shown in CS Figure 53. The difference between plots has potential implications for parametric modelling of ToT.

[redacted]

60

CS Table 60 (reproduced in Xxxxxx63 below for reference) presents AIC and BIC values entitled “Summary of goodness-of-fit data for dostarlimab ToT (GARNET ITT population) standard parametric and spline models”. However these values actually refer to models for the efficacy population detailed in the economic model. AIC/BIC values for the ERG’s parametric modelling of the ITT data supplied in clarification is shown in Table 64. These values and ranking differ somewhat from those in CS Table 60. Parametric models of ToT are summarised in Xxxxxxx61. Differences between ITT and efficacy models are modest but are most pronounced over the first 2 years of modelling (i.e. that part most relevant to the company’s modelling). Of the ERG models the best fit to the first one year and first two years of the ITT KM is provided by the ggamma model.

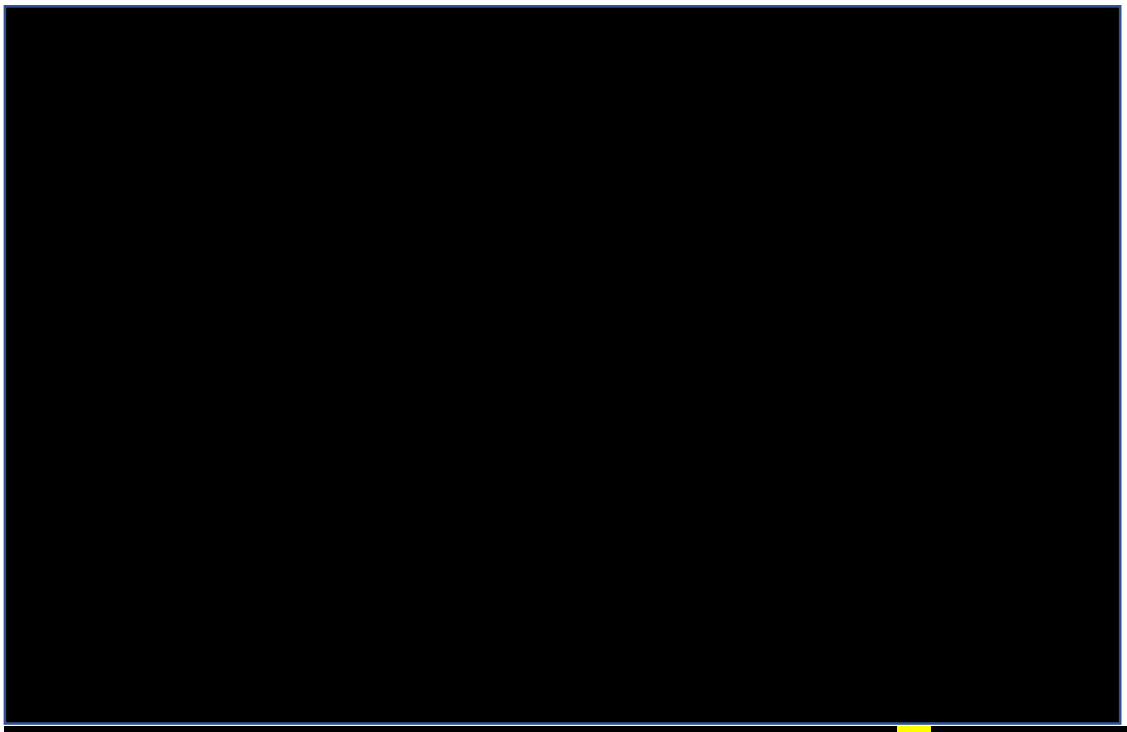
[redacted] 63 [redacted]

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Standard parametric models				
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard with single knot	[redacted]	[redacted]	[redacted]	[redacted]
Spline hazard with two knots	[redacted]	[redacted]	[redacted]	[redacted]

[a] A small AIC or BIC value represents a better goodness of fit.

Table 64: AIC/BIC values for the ERG's parametric modelling of the GARNET ITT data for ToT

Model	AIC	BIC	AIC/BIC aggregate	rank	Observations
ggamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R1P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



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9.5.1 Expert clinical opinion on ToT

The company's justification for their method of modelling ToT is said to be supported by the opinion of clinical experts who undertook a GSK consultancy exercise; in clarification the ERG requested details of the exercise. The CS states: "*UK clinical expert opinion indicates that, regardless of whether patients are continuing to derive clinical benefit from dostarlimab, they would likely not receive dostarlimab any longer than* [redacted]*: any patients still receiving dostarlimab at* [redacted] *were assumed to discontinue treatment at this point in the base case cost-effectiveness analysis. Long-term extrapolations beyond* [redacted] *for ToT for dostarlimab were therefore not required*". However the ERG have been unable to identify clinicians' responses within the clarification consultation exercise details that can fully justify this statement.

In the exercise clinicians were shown a graph and a Table of data about time on treatment (shown in Xxxxxxx62 below); it is difficult to evaluate these because it is

described as “[redacted]” and how this data was constructed is unclear. In particular in shows ~[redacted] in treatment at ~ [redacted]

62 [redacted]

Clinicians were asked:

“[redacted]. The ERG believe the trajectory referred to is that used for “[redacted]” as shown in the graph above, however the graph trajectory stops at weeks 49-54 with about [redacted] in treatment (in contrast the GARNET trial data shows [redacted] in treatment at 52 weeks). The figure of [redacted] in the table at [redacted] appears to be a value “suggested” to the clinicians as a possibility. Extrapolation of the trajectory in the [redacted] would be difficult to gauge and the validity of any estimates doubtful because the origin and nature of the data is unclear. The ERG have not been able to identify clinicians’ quantitative responses to this question that might justify the company contention that in clinicians’ opinion patients would not receive dostarlimab beyond [redacted].

At time points after [redacted] the tabulated "[redacted]" provided to the clinicians does not align closely to the results observed in GARNET (e.g. KM plot shown in CS Figure 53) as shown below in Figure 63. The illustrative data shown to clinicians departs from the ToT KM at about [redacted]. The same considerations do not apply however when the company has analysed OS and PFS.

Figure 63: Comparison of GARNET ToT KM plot and data shown to clinical experts during elicitation exercise

The company further state that "*Accordingly, UK clinical experts indicated that based on their clinical experience with other I-O therapies, they would expect the real-world percentage of patients receiving dostarlimab after* [redacted] *would likely be between* [redacted]*% and* [redacted]*%, notably lower than the* [redacted]*% predicted by the GARNET ToT KM curve, and the percentages of patients on treatment at* [redacted] *predicted by all of the long-term extrapolations presented in [CS Figure 53]".* Again the ERG were unable to find clinicians' quantitative responses to support these values ([redacted] and [redacted]

Further questions posed for clinical experts were:

A]

[redacted]B]

"[redacted]The ERG note the wide range of clinicians' responses.

The ERG opinion is that the clinical experts' answers to structured questions posed in the consultancy exercise do not precisely support the company's modelling of ToT as shown in CS Figure 54, but may reflect the company's interpretation of clinicians narrative responses obtained during consultancy.

The company partly justify their ToT model on the basis that a similar clinician-opinion led model has been accepted by the avelumab appraisal committee. For the avelumab appraisal (TA517) a 2 year reduction to 33% remaining in treatment (rather than to [redacted] was implemented. The sponsors in that submission stated: "*Expert opinion was sought from three clinicians to establish how avelumab would be expected to be administered in practice, based on clinician experience of immunooncology therapies in other indications (such as ipilimumab, nivolumab and pembrolizumab)"* and "*In the model it has been assumed that the majority of patients cease treatment at 2 years. XXXXX XXXXX XXXXX both agreed that it was reasonable for a third of patients to remain on treatment after this time, with XXXXX XXXXX suggesting a realistic estimate would be between 30% and 40%. All clinicians agreed that a maximum treatment duration of 5 years, after which time all patients cease treatment, is reasonable. Furthermore, XXXXX XXXXX predicted that, based on melanoma data, continued treatment benefit would be observed* ". It is perhaps surprising that for modelling ToT with dostarlimab that GSK

applied such a large effect at [redacted] reducing proportion in treatment to only [redacted] The ERG consulted TA517 NICE documents but the observed PFS KM plot was one of many items completely redacted.

In view of this critique of the ToT modelling the ERG prefer a model that [a] is based on ITT population, rather than efficacy population; [b] uses the ggamma model for years [redacted], since this provides a superior fit to the KM data at times up to both [redacted] and [redacted]; [c] implements a reduction in the proportion in treatment to a larger value than the company's [redacted] at [redacted], since this seems more consistent with information available from the consultancy exercise; [d] continuation of the ggamma model to be in line with NICE appraisal committee for avelumab to year 5 years when all treatment is discontinued. To indicate the impact of selecting a higher value than [redacted] for exploratory illustration purposes the ERG looked at 27% at [redacted] (an arbitrary intermediate value between the company's [redacted]% and the 33% accepted by the TA 517 appraisal committee). Resulting models are shown in Xxxxxxx64 and compared with models with reduction to [redacted] on treatment at [redacted]. Weibull models generated in the same way are shown in Xxxxxxx65.

The economic impact of alternative ToT models to the base case CS model may be appreciable.

64

65

9.6 *Hazard plots for the company's parametric models of OS of patients receiving dostarlimab*

[redacted]66 left shows the hazards of the company's unadjusted parametric models extrapolated to 40 years. Taking modelled hazard as an indicator of risk of death for the ageing GARNET population it appears that, with the exception of Weibull, exponential and gamma models, risk of death continuously decreases through time. With treatment-waning adjustment for waning ([redacted]66 right) again with the exception of Weibull, exponential and gamma models, the risk of death decreases with time from [redacted] on. Decreasing hazard over such a 40 year extended period seems rather implausible in the context of ageing human populations which generally experience increasing risk of death with ageing over such extended time scales.

[redacted]

66

[redacted]67 below compares hazard of the CS treatment-waning adjusted ggamma model with hazard for the company's age-matched general population. To align with the

company's ggamma model, the matched general population hazard is based on the well-fitting Gompertz parametric model for the matched population. Hazard from the ggamma model is more than ten times less than that for the general population from about [redacted] onward.

[redacted] 67

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 2 August 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

SECTION 1: Issues relating to model assumptions and approaches

Issue 1 ERG critique of the company cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.1, Page 118 The ERG report notes *"The ERG rebuild has identified one major error and a number of more minor errors in the company model structure."* Section 4.3.1, Page 118 The ERG report notes "*But the intervening sections work with the £68,376 per QALY ICER, which the ERG will refer to as the ERG corrected company base case. The ERG thinks that the ERG corrected company base case" is the more relevant figure to work with."* Section 1.1, Page 16 *"A key difference between the company's preferred assumptions and the ERG's preferred assumptions is whether there are errors in the model implementation. The ERG reports the company base case ICER of £50,221 per quality adjusted life*	"The ERG rebuild has **incorporated a number of alternative preferences compared to the company cost-effectiveness model**." "But the intervening sections work with the £68,376 per QALY ICER, which the ERG will refer to as **the ERG preferred company base case. The ERG thinks that the ERG preferred company base case** is the more relevant figure to work with." "A key difference between the company's preferred assumptions and the ERG's preferred assumptions is whether there are errors in the model implementation. The ERG reports the company base case ICER of £50,221 per quality adjusted life year (QALY), but for most of its commentary of Chapter 4 it references the **ERG preferred company base case** ICER of £68,376 per QALY."	Of the list of changes detailed in Section 4.3.1, the majority represent alternative modelling approaches and differences of opinion between the company and the ERG, and therefore it is inaccurate to refer to the majority of these changes as the corrections of errors: • The calculation of treatment waning and the equalising of dostarlimab effectiveness with the comparator RWEQ effectiveness is not an error, but a simplifying assumption applied by the Company, while an alternative approach was applied by the ERG. As discussed in Issue 3, below, the Company acknowledges the ERG's approach is appropriate, but notes that the original approach was not an error. • The model assumes 3 weekly dosing of dostarlimab, when from the 5th administration, dostarlimab will be administered once every six weeks. As	No factual error. No revision required.

year (QALY), but for most of its commentary of Chapter 4 it references the ERG corrected company base case ICER of £68,376 per QALY."		discussed in Issue 2, the original approach applied was a simplifying assumption. The Company acknowledges the ERG's approach may be appropriate once the ERG have updated their model to apply dostarlimab administration costs once every two cycles (six weeks) – the current model applies dostarlimab administration costs once every cycle (three weeks) and overestimates the costs associated with dostarlimab. • As discussed in Issue 4, the subsequent treatment assumptions in the Company model should already be considered conservative. • As discussed in Issue 5, the Company's decision to exclude cisplatin plus doxorubicin was a reasonable decision, based on a selection of a 5.0% cut off threshold; while the ERG may have an alternative preference, it is misleading to denote the Company's approach as *"peculiar and an error of judgement".*	

		Accordingly, it is inaccurate to refer to the resulting ICER from the list of changes as the ERG *corrected* ICER, when the majority of the changes reflect the incorporation of the ERG's preferred assumptions. Therefore, the Company would like to request that this list of alternative modelling approaches, and the resulting updated ICER, are denoted as the ERG's preferred company base case accordingly throughout the report where relevant, including in this section as well as the executive summary and any other relevant sections.	

Issue 2 Modelling of dostarlimab administration costs in the ERG's model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.1, Page 118 The ERG report notes "The model assumes 3 weekly dosing of dostarlimab when from the 5th administration it is 6 weekly. Correcting this error worsens the company base case ICER from £50,221 per QALY to £52,591 per QALY."	"The model assumes 3 weekly dosing of dostarlimab when from the 5th administration it is 6 weekly. **Implementing the ERG's preferred methodology changes the company base case ICER from £50,221 per QALY to £51,310** per QALY".	The ICERs presented by the ERG throughout the report which incorporate the ERG's preferred methodology for the dostarlimab costs (such as Executive Summary Section 1.7, Table 3 and Table 4, Section 5.3 Table 43, Table 44 and Table 48) are overestimated. The ERG report notes that the model has been updated to consider six weekly administration of dostarlimab. However, the	The ERG accepts the error and has corrected the ICER for the ERG corrected company base case and all ICERs that hang off the ERG corrected company base case. The ERG has also supplied the company with a corrected ERG revised company model.

		ERG's model applies administration costs for dostarlimab in each three weekly cycle which is twice as often as the administration costs should be applied according to a six weekly dosing schedule, meaning that the ERG's updated model overestimates the administration costs that should be associated with dostarlimab. Once this is corrected so that administration costs for dostarlimab are only applied once every two cycles (six weeks) in the ERG's model, the updated ICER using the ERG's preferred methodology for dostarlimab administration equals £51,310, rather than £52,591. Furthermore, it should be noted that in the Company submission (CS) a simplifying assumption was made whereby patients incurred 0.5 doses of dostarlimab during each three-weekly cycle, rather than 1 dose in every two cycles. The Company acknowledges that the ERG's approach may be appropriate (assuming dostarlimab administration costs are only applied once every two cycles to reflect a six weekly dosing schedule) but would like to request that the ERG report is updated to	The ERG revised model suggests an ICER of £51,310 per QALY with this corrected.

		denote that this was not an error in the company base case but a simplifying assumption.	

Issue 3 Application of treatment waning

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.1, Page 118 The ERG report notes *"The major error is the calculation of treatment waning and the equalizing of dostarlimab effectiveness with the comparator RWEQ effectiveness as reviewed in greater detail in section 4.3.1.1 below. Correcting this error worsens the company base case ICER from £50,221 per QALY to £62,804 per QALY".* Section 6.1.1, Page 149 The ERG report notes: *"Due to the company error the company submission presentation of the OS curves adjusted for waning is also incorrect."*	"**The ERG have incorporated an alternative approach for** the calculation of treatment waning and the equalisation of dostarlimab effectiveness with the comparator RWEQ effectiveness as reviewed in greater detail in section 4.3.1.1 below. Incorporating this methodology worsens the company base case ICER from £50,221 per QALY to £62,804 per QALY". "**The ERG would prefer to incorporate an alternative approach to treatment waning, which results in alternative OS curves compared to the company submission**".	It is inaccurate to refer to the Company's treatment waning approach as a major error – the approaches proposed by the Company and the ERG are fundamentally different . The hazard ratio treatment waning methodology applied in the base case cost-effectiveness analysis was adopted as a simplification, due to limited past precedent for treatment waning when a hazard ratio is not considered appropriate to use to model the comparator arm. The Company agree that the ERG's alternative methodology is appropriate, however, it is inaccurate to refer to the original approach as a major error, and would like to request that the ERG report is updated accordingly.	No factual error. No revision required.

Issue 4 Modelling of subsequent treatments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.1, Page 118 The ERG report notes *"The company model assumes that dostarlimab patients who receive a subsequent treatment receive only 1 subsequent treatment while the GARNET trial data suggests more than 1 subsequent treatment. Correcting this error worsens the company base case ICER from £50,221 per QALY to £50,731 per QALY."*	"The company model assumes that dostarlimab patients who receive a subsequent treatment receive only 1 subsequent treatment while the GARNET trial data suggests more than 1 subsequent treatment. **Implementing the ERG's preferred alternative assumption** worsens the company base case ICER from £50,221 per QALY to £50,731 per QALY."	The ERG's preferred assumption is to apply the average number of subsequent treatments for dostarlimab based on GARNET, as the source of clinical effectiveness estimates. It is inaccurate to state that the approach taken by the Company is an error in the company's model; both the company's and ERG's approaches to modelling subsequent treatments reflect alternative simplifying assumptions, in the absence of data on the subsequent treatments that patients would receive following treatment with dostarlimab in UK clinical practice. The Company's methodology for modelling subsequent treatments was already conservative, and assumed that [redacted]% ([redacted]) of patients would receive subsequent treatment following dostarlimab (by considering only the percentage of patients who had completed treatment with dostarlimab at the time of the data cut-off), when only [redacted]% ([redacted]) of patients received	No factual error. No revision required.

		subsequent treatment in the GARNET trial overall. While the ERG's preferred methodology might be to use an even more conservative adjustment, it is inaccurate to denote this as an error in the Company's model. This is particularly pertinent when considering the uncertainty around the subsequent treatment distributions in the GARNET trial – for example, there are no data on the duration of any of the listed subsequent treatments, and it is possible that a patient may have received one treatment and then immediately switched to another, whereas the ERG assume each patient would be treated with 1.4 full regimens of subsequent therapy. Furthermore, the generalisability of the GARNET subsequent treatment data is a possible concern. There is no consensus regarding the standard of care for subsequent treatments in the UK for patients with recurrent or advanced EC who have progressed on or after platinum-based chemotherapy and one further treatment in UK clinical practice, and as patients were recruited from around the world in	

		the GARNET trial, and there is a lack of evidence about how well the subsequent treatment distribution is generalisable to UK clinical practice. Given this uncertainty associated with the ERG's preferred assumption, the Company request that the ERG report is updated to note that this is simply the ERG's preferred assumption, and not an error in the company's model.	

Issue 5 Exclusion of cisplatin plus doxorubicin

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.1, Page 118 The ERG report notes: *"While not a modelling error the company excludes doxorubicin + cisplatin from the RWEQ costing on the basis of it comprising less than 5% of those treated, but at [redacted]% ([redacted]) this is peculiar and the ERG thinks it an error of judgement. But including doxorubicin + cisplatin has minimal effect upon the company base case, worsening the company base case ICER from*	"While not a modelling error, the company excludes doxorubicin + cisplatin from the RWEQ costing on the basis of it comprising less than 5% of those treated. **The ERG prefers to consider a lower cut-off threshold than 5% and accordingly includes doxorubicin plus cisplatin,** which has a minimal effect upon the company base case ICER from £50,221 per QALY to £50,368 per QALY." "Note that the company ~~declined to~~ **did not** supply the KM curve for cisplatin + doxorubicin ~~mainly~~ due to it falling marginally below the ~~arbitrary~~ 5% of RWEQ patients threshold that	It is misleading to denote the company's approach here as "*peculiar and an error of judgement*", and while the ERG states that this is not "*a modelling error*", this is listed in a bullet pointed list which is introduced with "*The ERG rebuild has identified one major error and a number of more minor errors in the company model structure*." As such, the Company would like to request that the ERG report is updated to denote that this is a difference in approach between the	No factual error. No revision required.

£50,221 per QALY to £50,368 per QALY." Section 4.3.3.6, Page 134 The ERG report notes: *"Note that the company declined to supply the KM curve for cisplatin + doxorubicin mainly due to it falling marginally below the arbitrary 5% of RWEQ patients threshold that the company uses for costing purposes ([redacted])"*	the company uses for costing purposes ([redacted])"	Company and the ERG. It is an alternative preference for the cut-off point for whether a treatment regimen was included/excluded – the CS also uses this 5% threshold when determining whether AEs should be included in the model (Grade 3 and above AEs experienced in more than 5% of patients were included). Once this cut-off threshold is selected, it would be inappropriate to disregard this and include cisplatin plus doxorubicin regardless. This is particularly true when considering that cisplatin plus doxorubicin was not specifically listed in the NICE final scope. Similarly, wherever the ERG's alternative cut-off preference is mentioned throughout the report, it is misleading to suggest that the Company's choice of cut-off is incorrect; this should be updated accordingly throughout the report, or justified as to why it is believed to be incorrect.	

Issue 6 GARNET population characteristics

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 46, The ERG report states (referring to the GARNET ITT population) "[redacted] *patients received more than 2 prior lines of anticancer therapy for recurrent or advanced disease, which is not in accordance with the specified inclusion criteria of no more than 2 prior lines of anticancer therapy (CS Appendix N). The company did not provide justification for this inclusion. The ERG considered the inclusion of these* [redacted] *patients important as it is unclear if any adjustments were made in the indirect comparisons."*	Please could the ERG report be amended to reflect the reasoning as to why patients could receive more than 2 lines of prior therapy whilst still satisfying the trial inclusion criteria: "Overall, [redacted] patients received more than 2 prior lines of anti-cancer therapy for recurrent or advanced disease. **These patients still satisfied the trial inclusion criteria as only platinum-based therapies were included in the trial inclusion criteria; other anti-cancer therapies, such as non platinum-based chemotherapies (e.g. doxorubicin) or hormone therapies, were not considered as prior lines of anti-cancer therapy in the trial inclusion criteria (CS Appendix N.1).** ~~**which is not in accordance with the specified inclusion criteria of no more than 2 prior lines of anticancer therapy (CS Appendix N). The company did not provide justification for this inclusion.The ERG considered the inclusion of these [redacted] patients important**~~	The discrepancy identified by the ERG is due to a difference in the definition of anti-cancer therapy in the inclusion criteria of the trial and the protocol. Table 7 of the CS uses the definition "prior lines of therapy", which is inclusive of all anti-cancer treatments, such as platinum or non platinum-based chemotherapies, or other anti-cancer treatments such as hormone therapy. Whereas the trial inclusion criteria (Appendix N.1 of the CS) related to platinum-based chemotherapy only, specifically that patients must have received no more than 2 lines of platinum-based chemotherapy to be eligible for the GARNET trial. As such, the [redacted] patients recorded as having 3 or more lines of prior therapy could have received up to 2 lines of platinum-based therapy, plus further non-platinum-based therapy, such as hormone therapy. These patients would still satisfy the trial inclusion criteria of no more than 2 lines of anti-cancer therapy.	No factual error, but in response to the further information provided by the company, ERG has amended the text to read: "15 (11.6%) patients received more than 2 prior lines of anticancer therapy for recurrent or advanced disease, which appear to contradict with the specified inclusion criteria of no more than 2 prior lines of anticancer therapy (CS Appendix N). The company explained in factual accuracy check that the 2 prior lines of anticancer therapy for trial inclusion refer specially to platinum-based therapy, However the ERG could not verify this based on the published trial protocol." It remains unclear if the recently highlighted difference in the definitions of anti-cancer therapy in the inclusion criteria of the trial and in the CS was established post hoc, given the fact that it was not noted in the earlier company's response to the ERG's clarification question A15.

	~~as it is unclear if any adjustments were made in the indirect comparisons.~~	Considering this, no patients were removed from the GARNET sample due to the numbers of lines of prior anti-cancer therapy for the purposes of matching the GARNET population as part of any indirect comparisons, except for any instances where the comparator study specifically stated that patients only received one prior line of platinum-based chemotherapy (in which case, patients who received two lines of platinum-based chemotherapy prior to dostarlimab in the GARNET trial were removed for matching).	This difference in definition also leads to further uncertainty; for example, it is unclear if patients with 2 prior lines of anti-cancer therapy in CS Table 7, received 2 platinum-based therapies or 1 platinum-based therapy and 1 non platinum-based chemotherapy.

Issue 7 Discussion of the company's TTD expert elicitation process

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 128, Section 4.3.3.3 *"The ERG thinks that to elicit the desired result the company has presented an invalid data set that appears to show a smooth steady fall in the number of patients remaining on dostarlimab"*	~~"The ERG thinks that to elicit the desired result the company has presented an invalid data set that appears to show a smooth steady fall in the number of patients remaining on dostarlimab"~~	At the time of this advisory board, the Kaplan Meier TTD S(t) curve was not available to the Company. The presentation of the KM numbers remaining at risk was therefore the best option available to the Company at the time this pre-scheduled advisory board was conducted in order to best inform the duration of dostarlimab	No factual error. No revision required.

		treatment in the cost-effectiveness model. It is also important to note that while the presentation of the Kaplan Meier TTD S(t) curve may have been appropriate, had it been available at the time of the advisory board, the Kaplan Meier curve is not without its own limitations, considering that very few patients were at risk in the tail of the KM curve. It is therefore inaccurate to suggest that "*in order to elicit the desired result, the company has presented an invalid data set*", and the Company would like to request that ERG report is updated to reflect a factual account of the advisory board and the expert elicitation.	

Issue 8 Discussion of the company's TTD expert elicitation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 130, Section 4.3.3.3 *"It is unclear whether either of these experts were either of the two of seven experts who tended to disagree with the pre-specified*	*"**As the polling responses during the advisory board were collected anonymously**, both the company and the ERG are unclear whether either of these experts were either of the two of seven experts who tended to disagree with the*	The context of this statement is misleading, and could be interpreted to suggest that the Company intentionally selected the experts for subsequent one to one interviews based on their responses during the advisory board.	No factual error. No revision required.

responses of the main elicitation exercise"	*pre-specified responses of the main elicitation exercise"*	This is inaccurate, given the anonymised nature of the polling questions during the ad-board, which were collected as anonymised responses using Slido, as previously detailed. As such, this statement should be amended accordingly.	

Issue 9 The ERG's preferred TTD estimates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 131, Section 4.3.3.3 The ERG report notes: *"Given this the ERG will apply a percentage of [redacted]% and will explore [redacted]% and [redacted]%. In the light of the SmPC the ERG will constrain the proportion on treatment after the first cessation point to be the lesser of the TTD curve and the PFS curve."*	Please could the ERG provide additional details on how their preferred estimates have been derived, as well as additional justification for why this might represent a more robust methodology versus the Company's assumptions? Currently, it is not clear how the values of [redacted]% and [redacted]% have been derived.	The Company do not believe that the ERG have provided clear rationale for the derivation of the [redacted]% or [redacted]% estimates included in the ERG's preferred base case estimates. Accordingly, please could the ERG provide additional details about how these values have been derived as well as justification for why these assumptions are more robust compared to the Company's base case estimate?	No factual error. No revision required.

Issue 10 Description of the ERG's preferred treatment waning approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 131, Section 4.3.3.3 The ERG report notes: "*A treatment benefit is still assumed for [redacted] after treatment cessation, which in itself may be optimistic.*"	"A treatment benefit is still assumed for [redacted] after treatment cessation, ~~which in itself may be optimistic~~."	It is misleading to suggest that the ERG's preferred assumptions may be optimistic without additionally presenting a balanced viewpoint or justification about why the ERG believes their assumptions are optimistic. It should be noted that the Company's original base case treatment waning assumptions were already conservative, and likely underestimated the efficacy associated with dostarlimab. In the Company's model, following the first cessation point, any patients remaining on treatment with dostarlimab continue to incur the full costs associated with treatment, but from [redacted] after the first cessation point, treatment waning is applied to all patients, including those who still remain on treatment. This likely underestimates the overall efficacy associated with dostarlimab, as treatment waning would only impact patients who have discontinued dostarlimab in clinical practice. The ERG's approach further accentuates the above point. The ERG assume that a larger [redacted]% of patients continue to receive treatment with dostarlimab after [redacted]	No factual error. No revision required.

		[redacted], yet the ERG also applies treatment waning earlier than the Company's model, immediately after the first cessation point for all patients, irrespective of whether they remain on treatment or not. The ERG thereby assume that the efficacy associated with dostarlimab begins to decline immediately for all patients, including the [redacted]% of patients who are still receiving dostarlimab without any change to their dosing schedule. This is an extremely conservative assumption, and likely results in a marked underestimation of the efficacy associated with dostarlimab. From [redacted], the ERG assume that there is no incremental efficacy associated with dostarlimab compared to current clinical management for any patient, even though a non-negligible number of patients will have only just discontinued dostarlimab at [redacted], and therefore would only be expected to experience treatment waning from [redacted], instead of experiencing no incremental benefit associated with dostarlimab compared to current clinical management after Year 5 (which is what is currently modelled). While the exact duration of treatment waning varies between the Company's and ERG's preferred assumptions, both approaches assume that patients who discontinue	

		dostarlimab at [redacted] would experience some incremental benefit associated with dostarlimab versus current clinical management until [redacted]. Considering the conservative nature of the ERG's preferred assumptions, the Company believe that this statement is misleading without presentation of a balanced viewpoint, or additional justification regarding why the ERG believe this assumption is optimistic, considering the above.	

Issue 11 Choice of dostarlimab TTD curve

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.3.8, Page 138 The ERG report notes: "*Since the dostarlimab TTD curve is mainly being applied prior to the first cessation point and so during the period for which Kaplan Meier data is available, there is less need to assess the reasonableness of extrapolation.*"	Since the dostarlimab TTD curve is mainly being applied prior to the first cessation point and so during the period for which Kaplan Meier data is available, there is less need to assess the reasonableness of extrapolation. **However, the number of patients receiving treatment following the first cessation point is still derived from the chosen parametric extrapolation (with the adjustment applied), and consequently the plausibility of**	It is inaccurate to state that the dostarlimab TTD curve is mainly applied prior to the first cessation point. Whilst the TTD curve is adjusted at the first cessation point, the subsequent numbers of patients on treatment is still based on the adjusted TTD curve until all patients discontinue dostarlimab, and therefore, it is still important to consider the subsequent TTD curve extrapolation.	No factual error. No revision required.

	each extrapolation should still be considered.		

Issue 12 Justification for the ERG's TTD curve

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 126 of the ERG report states *"The ERG Kaplan Meier % N at risk are typically higher than those of the company. It is difficult to know quite what data points the company presentation relates to as some span periods up to 6 weeks, but even given this the ERG cannot align its N at risk with that of the company presentation."*	Please could the ERG provide additional details and clarification on how the TTD KM curve for dostarlimab was estimated.	It is currently unclear how the ERG estimated the TTD curve and % N at risk for dostarlimab. Therefore, the Company cannot provide further clarification as to why the ERG cannot align its % N at risk with the CS. Please could the ERG report be amended to include further detail on how this was estimated.	No factual error. No revision required. The ERG TTD KM curve was constructed in the usual fashion using the KM data supplied by the company at clarification. The ERG has supplied a copy of the calculations for the TTD curve alongside its revised economic model.

Issue 13 Discussion about the number of patients at risk for TTD in GARNET

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 126 of the ERG report states *"The reason for the anomalous increase from [redacted] for 31w-36wpatients to [redacted] patients for 37w-42w in the company presentation is unclear"*	Please can this sentence be removed from the ERG report. ~~**The reason for the anomalous increase from [redacted] for 31w-36wpatients to [redacted] patients for**~~	The increase from [redacted] to [redacted] patients at risk is not anomalous but is instead because of the inclusion of patients who had a delayed dose, rather than just discontinued. If a patient received a delayed dose, they were included in the next interval in which they then received	The ERG has revised the ERG report accordingly.

	~~37w-42w in the company presentation is unclear.~~	the 'delayed' dose. This explains the increase in patient numbers.	

Issue 14 Incorporation of time to death variables

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.4.1, Page 139–140 The ERG report notes: *"Given the centrality of the PFS and PPS health states to the model the ERG thinks it is peculiar to introduce the time to death variable if this renders the PPS coefficient not statistically significant."*	Given the centrality of the PFS and PPS health states to the model **the ERG would prefer to not include the** time to death variable if this renders the PPS coefficient not statistically significant.	While the ERG may have an alternative preference with regard to the use of the time to death variable, it is inaccurate to state that the company approach is peculiar as a result. The Company would like to request that this statement is updated accordingly.	No factual error. No revision required.

Issue 15 Incorrectly reported results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 50: ERG base case: Disaggregate costs on page 151 of the ERG report contains incorrect results.	Please could the values be amended as follows: RWEQ / DOST / Net Diagnostic Drug + admin AEs PFS ongoing	The diagnostic costs should be £[redacted] and the results in all subsequent rows are incorrect due to being offset by one row.	The ERG has revised Table 50 accordingly.

	Subsequent Treatment PPS ongoing End of Life	[redacted]	[redacted]	[redacted]			
	Total	[redacted]	[redacted]	[redacted]			

Issue 16 Presentation of the company base case ICERs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Executive Summary Section 1.2, Table 2 Section 5.1, Page 143 The ERG reports the company base case in Table 2 and Table 38. Table 42 reports the results of the scenario analyses.	It should be noted that the results presented in Table 2/38 and throughout the ERG report are from the original company base case submission. An updated company base case was submitted in response to the ERG clarification questions, question B2, which should also be reported here. This will also affect the results of the scenario analyses presented in Table 42 of the ERG report. The revised results, which were presented in response to the ERG clarification questions (question B6), should be reported here.	The most recent company base case analysis should be reported here, and used throughout the ERG's updated analyses. While the difference is minor, the updated results should be noted.	The ERG has presented the results of the updated company base case in the revised report.

Issue 17 Inclusion of RWEQ PLD costing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.4.5, Page 141 The ERG report notes *"It might have been more reasonable to assume a 50:50 split between dosing under and dosing over 70mg, which would slightly lessen the direct drug cost per 4 week treatment cycle from £1,425 to £1,248."*	"**The ERG would have preferred to assume a** 50:50 split between dosing under and dosing over 70mg, which would slightly lessen the direct drug cost per 4 week treatment cycle from £1,425 to £1,248."	It could be considered misleading to suggest that the ERG's arbitrary assumption would be more reasonable than the use of the dosage calculated using the mean patient characteristics of patients in the GARNET trial. As such, this section should be updated to note that this would simply be the ERG's preference.	No factual error. No revision required.

Issue 18 Prevalence associated with screening costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.2.2, Page 124 The ERG report notes *"The ERG has not been able to source the 23% dMMR prevalence from the NICE DG42 impact report. This can be resolved during technical engagement."*	**The percentage of 23% dMMR prevalence has been derived from the percentage of patients having positive tests for PMS2, MSH2, MSH6 and MLH1 from the NICE DG42 resource impact report.**	This percentage is derived from the NICE DG42 resource impact report: • Patients having IHC testing who have positive results PMS2, MSH2 and MSH6 who go on to be offered genetic counselling for Lynch syndrome (a) = 5.8% • Patients having IHC testing who have a positive result for MLH1 = 16.7%	The ERG has deleted section 4.3.2.2 in the revised report.

		The sum of these two estimates from the NICE DG42 report is equal to 22.6%, which is rounded to 23%.	

Issue 19 Presentation of economic scenarios versus individual comparators using the MAIC hazard ratios

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Executive Summary Section 1.2, Page 17 The ERG report notes *"The company performs a number of comparisons with individual treatments using hazard ratios from the literature. One comparison with carboplatin + paclitaxel suggests that dostarlimab is dominated, another that the ICER is £106k per QALY. A range of comparisons with doxorubicin suggests ICERs of £63,144 per QALY, £55,284 per QALY, £41,337 per QALY and £40,439 per QALY. The comparison with carboplatin suggests an ICER of £65,367, while the comparison with paclitaxel suggests an ICER of £56,911 per QALY."*	"**The company performs a number of comparisons with individual treatments using comparator efficacy data derived from the literature and HRs which were estimated by the Company through the conduct of several MAICs.** One comparison with carboplatin + paclitaxel suggests that dostarlimab is dominated, another that the ICER is £106k per QALY. A range of comparisons with doxorubicin suggests ICERs of £63,144 per QALY, £55,284 per QALY, £41,337 per QALY and £40,439 per QALY. The comparison with carboplatin suggests an ICER of £65,367, while the comparison with paclitaxel suggests an ICER of £56,911 per QALY. **However, most of the MAICs based on the published literature were limited by small sample sizes and very limited matching information, and therefore the level of uncertainty associated**	It is inaccurate to state that the comparisons with individual treatments used hazard ratios from the literature; the report should note that these comparisons used hazard ratios which were calculated using comparator efficacy data from the published literature. When discussing the results of the MAICs, it is also important to note the associated uncertainty with these comparisons so that the reader is able to interpret these results with appropriate context, especially with regard to comparisons to carboplatin plus paclitaxel given the particularly small sample size, limited matching information and lack of statistically significant findings identified in these comparisons.	The text has been revised to read: "The company performs a number of comparisons with individual treatments using hazard ratios derived from the company's MAICs based on comparator effectiveness data from the literature."

	with the validity and representativeness of these findings is very high. In particular, given the above limitations and that the results for the MAICs with carboplatin plus paclitaxel were not statistically significant, the uncertainty associated with any scenarios based on these MAICs is particularly high, and should be interpreted with caution."		

Issue 20 Calculation of TTD percentage

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Appendix 9.5.1, Page 239 The ERG report notes *"To indicate the impact of selecting a higher value than [redacted]% for exploratory illustration purposes the ERG looked at [redacted]% at [redacted] (average of [redacted]% and the 33% accepted by the TA 517 appraisal committee)."*	To indicate the impact of selecting a higher value than [redacted]% for exploratory illustration purposes the ERG looked at [redacted]% at [redacted] (average of [redacted]% and the 33% accepted by the TA 517 appraisal committee). Any resulting analyses using the average of [redacted]% should be updated to use a value of [redacted]% instead.	The mean of [redacted]% and 33% is equal to [redacted]%. It is therefore unclear why the ERG have used the value of [redacted]% in their exploratory analyses here and additional context and explanation need to be provided.	Error noted. Text changed to: …for illustration purposes the ERG looked at 27% at [redacted] (an arbitrary intermediate value between the company's [redacted]% and the 33% accepted by the TA 517 appraisal committee).

Issue 21 Use of stopping rule terminology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.2, Page 96 The ERG report notes *"Unusually, and in part justified by the approach of TA571, the company imposes stopping rules for dostarlimab, assuming that at [redacted] all but [redacted]% of patients stop treatment and at [redacted] all patients stop treatment."* *"Due to the dostarlimab treatment stopping rules"* *Section 4.2.6, Page 97* The ERG report notes *"Unusually, given the assumptions about dostarlimab stopping rules"* Section 4.3.3.3, Page 126 The ERG report notes *"It is unclear whether the company is suggesting that if NICE approves dostarlimab that a stopping rule at [redacted] should be a part of the recommendation and funding."*	Unusually, and in part justified by the approach of TA571, the company **applied an adjustment to reflect the anticipated real-world prescribing of dostarlimab,** assuming that at [redacted] all but [redacted]% of patients stop treatment and at [redacted] all patients stop treatment." Due to the dostarlimab **time on treatment assumptions**. Unusually, given the assumptions about dostarlimab **time on treatment.**	The Company are not proposing that a two-year stopping rule for dostarlimab should be implemented As highlighted in the CS, page 154, the probability of remaining on treatment after two years was [redacted]%, based on the GARNET TTD KM curve. However, this was considered to be an overestimate and not representative of UK clinical practice, considering the KM curve has only [redacted] patients at risk beyond 21 months. UK clinical expert opinion indicated that a notably lower percentage of patients would likely remain on treatment with dostarlimab after two years. As such, the company applied an adjustment to the TTD curve from GARNET in order to reflect anticipated real-world prescribing more accurately. This is notably distinct from imposing a stopping rule for dostarlimab at [redacted], the Company would like to request the ERG's terminology is updated throughout the report to describe the Company's assumption more accurately.	No factual error. No revision required.

Issue 22 Representation of the company's expert elicitation process

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.3.2, Page 125-126 The ERG report notes: *"The key point is that the experts were never asked about the parameterised curves adjusted for dostarlimab treatment stopping rules. The OS and PFS elicitation exercises were conducted prior to the discussions around treatment stopping rules and treatment waning. It can be argued that the experts might have this in the back of their mind in any case, but the presentation of the unadjusted curves during the elicitation exercise suggests the opposite was anticipated by the company."* *The ERG thinks that the most reasonable interpretation of the company expert estimates for OS and PFS relate to the GARNET data and to the unadjusted curves. The ERG thinks that it is unreasonable for the company to have presented these results within its submission results overlaid on the dostarlimab*	The key point is that the experts were never asked about the parameterised curves adjusted for dostarlimab treatment stopping rules. The OS and PFS elicitation exercises were conducted prior to the discussions around treatment stopping rules and treatment waning. **However**, it can be argued that the experts might have this in the back of their mind in any case~~**, but the presentation of the unadjusted curves during the elicitation exercise suggests the opposite was anticipated by the company."**~~ The ERG thinks that the most reasonable interpretation of the company expert estimates for OS and PFS relate to the GARNET data and to the unadjusted curves. ~~**The ERG thinks that it is unreasonable for the company to have presented these results within its submission results overlaid on the dostarlimab adjusted curves. The ERG thinks that the company expert responses will be biased and too high for an assessment of the reasonableness of the adjusted curves.**~~	It is important to note that the expert elicitation questions explicitly asked experts to take into account their own clinical experience, and in doing so, it is unreasonable to suggest that the clinical experts would not have inherently considered their own time on treatment and treatment waning assumptions based on how they would expect dostarlimab to be used in clinical practice. It is misleading to suggest that clinicians would have assumed patients would receive treatment with dostarlimab indefinitely unless they were told otherwise, considering the limited treatment durations associated with other I-O therapies currently in use. Accordingly, the Company believes that the presentation of the unadjusted curves was the most reasonable approach, in order to avoid unduly influencing the experts and instead allowing them to provide answers based solely on the clinical trial data for dostarlimab and their own clinical experience and	No factual error. No revision required.

adjusted curves. The ERG thinks that the company expert responses will be biased and too high for an assessment of the reasonableness of the adjusted curves. Page 130-131 *Unbiased OS and PFS estimates adjusted for the TTD and treatment stopping rules obviously require prior consideration of the TTD and stopping rules.* Page 23, Section 1.5 The ERG report notes, *"The elicitation exercise concentrated upon the unadjusted curves. The ERG thinks this means it provides values for the unadjusted curves, but is not a good basis for selecting the adjusted curves"*	~~**Unbiased OS and PFS estimates adjusted for the TTD and treatment stopping rules obviously require prior consideration of the TTD and stopping rules.**~~ ~~**"The elicitation exercise concentrated upon the unadjusted curves. The ERG thinks this means it provides values for the unadjusted curves, but is not a good basis for selecting the adjusted curves"**~~	expectations, without introducing any potential bias. While the ERG may believe an alternative approach may have been appropriate, it is inaccurate to suggest the company's approach is biased and unreasonable and therefore the Company would like to request that the ERG report is updated to reflect a factual account of the advisory board and the expert elicitation. Further, it is incorrect to note that the Company's adjusted curves were selected solely based on the unadjusted curves presented during this expert elicitation process. The Company's curve selection process was based on the survival estimates provided by the clinicians, which, as discussed, would reasonably incorporate each clinician's own assumptions around long-term discontinuation and treatment waning associated with dostarlimab, in combination with the unadjusted data presented to them. The Company would like to request that this statement is removed accordingly.	

Issue 23 Consideration of mean time on treatment estimates without accounting for half cycle correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.4.3, Page 141 The ERG report notes: *The company also notes that the mean number of model cycles that patients remained on treatment within this was* [redacted]*. The company base case simulates a mean number of model cycles of* [redacted]*. This suggests reducing the modelled RWEQ drug and administration costs to* [redacted] *cycles; i.e. multiplying by a factor of 84%. This worsens the ERG corrected company base case ICER from £68,376 per QALY to £68,630 per QALY.* Executive Summary Section 1.7, Page 28 The results of SA07 presented by the ERG are based on the mean number of [redacted] above, instead of the half cycle corrected value of [redacted].	The company ~~**also**~~ notes that the ~~**mean**~~ **median** number of model cycles that patients remained on treatment within this was [redacted]. The company base case simulates a mean number of model cycles of [redacted] **(following the half-cycle correction applied in the base case analysis).** ~~This suggests reducing the modelled RWEQ drug and administration costs to [redacted] cycles; i.e. multiplying by a factor of **93**%. This worsens the ERG corrected company base case ICER from £68,376 per QALY to **£68,630** per QALY.~~	The ERG report incorrectly reports that the Company assumed a *mean* of [redacted] cycles of subsequent treatment in the dostarlimab arm from the RWE study, whereas this is in fact the *median* number of cycles. This median value was then used to model [redacted] cycles of subsequent treatment in the dostarlimab arm. Separately, TTD KM data from the RWE study were used to model time on treatment for the RWE comparator arm in the base case. Whilst the median number of cycles of treatment was [redacted], it is not unexpected that the mean number of cycles would differ, and is in fact [redacted] cycles (with the half-cycle correction applied). As such, the final sentence of this paragraph is not appropriate and incorrectly reports median and mean data. Nevertheless, it is also inaccurate to refer to a mean value of [redacted] model cycles here, as this value does not include the half cycle correction	ERG has replaced 'mean' with 'median' in the relevant text. Otherwise no factual error. No revision required. The drug costs within the model are based upon start of cycle proportions and not half cycle corrected proportions.

		applied in the Company's base case analysis. Please could the SA07 be removed and could ICERs be updated accordingly throughout the ERG report to include this correction.	

Issue 24 Carboplatin plus PLD administration costs in the ERG's model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6.2, Page 157 *The ERG report notes "The ERG has fitted curves to the RWEQ individual treatment KM data for carboplatin + paclitaxel, carboplatin + PLD and PLD monotherapy. These can be used to estimate the cost effectiveness of dostarlimab against the individual treatments."* *The cost effectiveness estimates for these are presented in Table 55.* The scenario versus carboplatin plus PLD presented by the ERG includes a simple administration cost of £241.06 in the first cycle, rather than the more	Please could the ERG update this scenario to incorporate the corrected complex administration cost for carboplatin plus PLD, and please could the relevant ICER be updated accordingly.	In line with the administration costs included for carboplatin plus paclitaxel, a complex administration cost should be applied for carboplatin plus PLD, a combination therapy.	The ERG has applied the complex administration costs for Carboplatin + PLD by increasing costs in this arm by £65.84 in the revised report.

appropriate complex cost of £306.90. The ERG do not present any justification for this assumption.			

Issue 25 Carboplatin plus PLD AE costs in the ERG's model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6.2, Page 157 *The ERG report notes "The ERG has fitted curves to the RWEQ individual treatment KM data for carboplatin + paclitaxel, carboplatin + PLD and PLD monotherapy. These can be used to estimate the cost effectiveness of dostarlimab against the individual treatments."* *The cost effectiveness estimates for these are presented in Table 55.* The ERG's scenario versus carboplatin plus PLD uses AEs, and associated costs and disutilities, for carboplatin monotherapy as a proxy for AEs for carboplatin plus PLD.	Please could the ERG update this scenario to include the more appropriate AEs, and associated costs and disutilities reported for carboplatin plus PLD from CALYPSO, 2012. Please could the resulting ICER, be updated accordingly.	Given the direct availability of AE data for carboplatin plus PLD from CALYPSO, 2012, it is not appropriate to use AE data from the same trial for carboplatin monotherapy as a proxy to model the AEs associated with carboplatin plus PLD.	The ERG has applied the AEs from CALYPSO for carboplatin plus PLD in the revised report.

These AEs are derived from CALYPSO, 2012, which also provides AE data for the combination of carboplatin plus PLD. The ERG do not provide any justification for this assumption.			

Issue 26 Lack of justification for use of stopping rule

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6.2, Page 157 *The ERG report notes "The ERG has fitted curves to the RWEQ individual treatment KM data for carboplatin + paclitaxel, carboplatin + PLD and PLD monotherapy. These can be used to estimate the cost effectiveness of dostarlimab against the individual treatments."* *The cost effectiveness estimates for these are presented in Table 55.* The ERG's scenarios versus individual treatments include a stopping rule for the comparator	Please could the ERG provide additional details and justification for the stopping rule incorporated in these scenarios versus individual comparators.	The TTD data for the UK RWE study show that some patients receive more than six cycles of chemotherapy in UK clinical practice, and therefore a stopping rule is potentially inappropriate here. It would be more appropriate to use the TTD data where available.	No factual error. No revision required. The ERG has simply adopted the company assumption as used for the individual treatment comparisons. If this is felt unreasonable it can be addressed at technical engagement in both the company analyses and the ERG analyses.

time to discontinuation curves (which are used as a proxy for time on treatment), whereby all patients are assumed to discontinue treatment after six cycles. The ERG do not provide any further justification for this assumption.			

SECTION 2: Typographical errors

Issue 27 Inaccurate statement regarding the EMA approval date

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30 of the ERG report states "*Dostarlimab has been approved by the European Medicines Agency (EMA) in February 2021"*	Please amend this to: Dostarlimab has been approved by the European Medicines Agency (EMA) in **April** 2021.	As presented on page 18 of the CS, EMA approval for dostarlimab was received in April 2021.	The ERG has amended the text.

Issue 28 Inaccurate statement regarding the GARNET trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30 of the ERG report *states "The primary evidence that supported the conditional marketing authorisation and that*	Please amend this to: The primary evidence that supported the conditional marketing authorisation and that forms the key part of clinical effectiveness evidence for dostarlimab in the CS for this	GARNET was a phase I trial.	The ERG has amended the text.

forms the key part of clinical effectiveness evidence for dostarlimab in the CS for this STA is data from a single arm phase I/II trial, Garnet"	STA is data from a single arm phase **I** trial, **GARNET.**		

Issue 29 Lack of additional context regarding hormone therapy evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34 of the ERG report states "*While hormone therapy was included in company's base case, no empirical data for its effectiveness was used as hormone therapy was not adequately captured in the registry. Instead, an assumption that its effectiveness is the same as other therapies in the basket of treatments was made."*	Please can this be amended to include the following additional detail: While hormone therapy was included in company's base case, no empirical data for its effectiveness was used as hormone therapy was not adequately captured in the registry **and the literature review did not identify any studies that provided relevant evidence**. **Instead, a conservative assumption that its effectiveness would be as good as the basket of chemotherapies was made, which was also validated by UK clinicians as being a reasonable assumption.**	Additional context for why the efficacy of hormone therapy had to be assumed to be similar to the basket of chemotherapy treatments is needed here.	While not a factual error, the ERG has added text to indicate that no relevant evidence was identified for hormone therapy from the literature review: "…*and the literature review did not identify any studies that provided relevant evidence. Instead, an assumption that its effectiveness would be as good as the basket of chemotherapies was made*."

Issue 30 Incorrect value reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 45 of the ERG report states "*GARNET is an ongoing multi-cohort study conducted in 8 countries"* Page 92 of the ERG report states *"The CS presents evidence from GARNET, a Phase 1, single-arm, open-label study of dostarlimab conducted in 8 countries (including 9 centres in UK)."*	Please can this be amended to GARNET is an ongoing multi-cohort study conducted in **9** countries" and "The CS presents evidence from GARNET, a Phase 1, single-arm, open-label study of dostarlimab conducted in **9** countries (including 9 centres in UK).	As reported in Table 6 on page 39 of the CS, GARNET had sites in 9 countries.	The ERG has amended the texts in both sections.

Issue 31 Unclear reporting of DOR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 9 on page 47 of the ERG report, it is not clear that the ERG are referring to median DOR.	Please specify that median DOR (min, max) is being referred to, as it has been done for PFS and OS, as follows: irDOR[c,e], **median (min, max)** [redacted]	Table 9 does not specify that the median DOR is being referred to. It has been specified for PFS and OS that the median is being used, so it is potentially misleading that this is not similarly specified for DOR and could imply that the ERG are referring to something other than the median (e.g. response events).	The ERG has amended the text.

Issue 32 Incorrect value reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51 of the ERG report states "*For the EQ-VAS, [redacted] participants had evaluable data.*"	Please amend this to: For the EQ-VAS, [redacted] participants had evaluable data.	As reported in Table 11 of the ERG clarification questions response, [redacted] patients were assessed for EQ-VAS at baseline in the GARNET ITT population. The value of [redacted] is the number of patients assessed for EORTC QLQ-C30.	The ERG has amended the text.

Issue 33 Unclear reporting of death data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51 of the ERG report states "*Death occurred in participants ([redacted]%) while in the study, with disease progression as the most common reason ([redacted]%).*"	Please amend this to: Death occurred in participants ([redacted]%) while in the study, with disease progression as the most common reason ([redacted]%).	If the ERG are referring to the percentage of deaths due to disease progression as the reason, then please amend this to [redacted]% (or [redacted]/129 ([redacted]%) out of the total number of patients in the GARNET trial). Alternatively, if the ERG are referring to the percentage of deaths due to disease progression during the treatment period only, please amend this value to [redacted].	The ERG has modified the text to provide additional clarification for the proportion of participants with disease progression associated with death out of the total number of patients in the GARNET trial: "*Death occurred in participants ([redacted]%) while in the study, with disease progression as the most common reason ([redacted]%).*"

Issue 34 Incorrect value reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 55 of the ERG report states "*However, patients with an ECOG PS of 'not recorded (NR)' (n=[redacted]) were not excluded by the company from the UK RWEQ cohort*"	Please amend this to: However, patients with an ECOG PS of 'not recorded (NR)' (n=[redacted]) were not excluded by the company from the UK RWEQ cohort.	As reported in Table 15 on page 55 of the CS, the total number of patients with ECOG PS NR in the GARNET-like RWE cohort was [redacted].	The ERG has amended the text.

Issue 35 Incorrect values reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 10 on page 58 of the ERG report contains incorrect values for the GARNET ITT population relating to histology at diagnosis.	Please amend this as follows: **Histology at diagnosis, n (%)** Endometrioid [redacted] Non-endometroid [redacted]	As reported in Table 7 on page 44 of the CS, the correct values for the proportion of patients with endometrioid and non-endometrioid disease at diagnosis in the GARNET ITT population are [redacted] and [redacted] respectively.	The data shown in Table 10 on page 58 of the ERG report were obtained from CS Appendix D, Table 37, page 100. The ERG has amended the text in the revised report as requested, but would welcome the company's clarification of the discrepancy between data presented in CS Table 7 and CS Appendix D Table 37.

Issue 36 Incorrect values reported

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Table 11 on page 66 of the ERG report contains a number of incorrect values in the following rows listed below (note only the relevant rows with incorrect values are listed):
<table>
<tr><th>Trial</th><th>Makker et al. (2013) N= 17)</th></tr>
<tr><td colspan="2">Race n (%)</td></tr>
<tr><td>White</td><td>16 (94.1)</td></tr>
<tr><td>Black</td><td>10 (16.7)</td></tr>
<tr><td colspan="2">Histology at diagnosis, n (%)</td></tr>
<tr><td>Endometrioid</td><td>NR</td></tr>
<tr><td>Non-endometrioid</td><td>NR</td></tr>
<tr><td>Missing</td><td>NR</td></tr>
<tr><td colspan="2">FIGO stage, n (%)</td></tr>
<tr><td>III</td><td>NR</td></tr>
<tr><td>IV</td><td>NR</td></tr>
</table>
<table>
<tr><th>Trial</th><th>McMeekin et al. (2015) (N=248)</th></tr>
<tr><td colspan="2">Performance status, n (%)</td></tr>
<tr><td>ECOG 0 (KPS 90-100)</td><td>86 (34.7)[c]</td></tr>
</table>
</td>
<td>Please can these values be amended as follows (correct values are marked in red):
<table>
<tr><th>Trial</th><th>Makker et al. (2013) N= 17)</th></tr>
<tr><td colspan="2">Race n (%)</td></tr>
<tr><td>White</td><td>16 (94.1)</td></tr>
<tr><td>Black</td><td>1 (5.9)</td></tr>
<tr><td colspan="2">Histology at diagnosis, n (%)</td></tr>
<tr><td>Endometrioid</td><td>5 (29.4)</td></tr>
<tr><td>Non-endometrioid</td><td>12 (70.9)</td></tr>
<tr><td>Missing</td><td>NR</td></tr>
<tr><td colspan="2">FIGO stage, n (%)</td></tr>
<tr><td>III</td><td>3 (17.6)</td></tr>
<tr><td>IV</td><td>14 (82.4)</td></tr>
</table>
<table>
<tr><th>Trial</th><th>McMeekin et al. (2015) (N=248)</th></tr>
<tr><td colspan="2">Performance status, n (%)</td></tr>
<tr><td>ECOG 0 (KPS 90-100)</td><td>86 (34.7)[c]</td></tr>
</table>
</td>
<td>Typographical errors.

The correct data are reported in Table 18 on page 61 of the CS appendices.</td>
<td>The ERG has amended the text for Makker et al. (2013).

The ERG notes that the company did not correctly match the KPS scale in McMeekin et al. (2015) to the respective ECOG status scale, and has made minor revisions on page 64:

“The company matched KPS scale in McMeekin et al. (2015) to ECOG status scale to align the performance measure across studies in this submission (see CS Appendix D.4.3,Table 19); however, KPS 90, 80, 70 and 60 were mismatched to their respective ECOG status. The ERG matched the performance scales (see Table 11 below) using the guidance provided by the ECOG-ACRIN Cancer Research Group.”

The ERG has revised the proportions for the performance status in McMeekin et al. (2015) on Table 11, page 66.

For GARNET ITT, the data shown in ERG Table 11 are consistent</td>
</tr>
</table>

ECOG 1 (KPS 70-80)	95 (38.3)[c]	ECOG 1 (KPS 70-80)	**79 (32)[c]**		with what were reported in CS Table 7 and CS Appendix D Table 37, whereas the data quoted in the company's factual accuracy check seem to come from CS Table 15. The ERG notes that the data reported in CS Table 7 and CS Appendix D Table 37 are not consistent with those reported in CS Table 15, and would welcome the company's further clarification with regard to which dataset is correct.
ECOG 2 (KPS (50-60)	66 (26.6)[c]	ECOG 2 (KPS (50-60)	**64 (25.8)[c]**		
Trial	**GARNET ITT population (N=129)**	**Trial**	**GARNET ITT population (N=129)**		
Grade of disease at diagnosis, n (5)		**Grade of disease at diagnosis, n (5)**			
Grade 4	[redacted]	Grade 4	[redacted]		
Not assessable	[redacted]	Not assessable	[redacted]		
Missing	[redacted]	Missing	[redacted]		

Issue 37 Incorrect values reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 11 on pages 67 and 68 of the ERG report contains the following values, some of which are incorrect: **Trial** / **GARNET-like UK RWE (RWEQ) cohort (N[redacted]** / **GARNET-like UK RWE (RWEQ) - PLD monotherapy**	Please can these values be amended as follows: **Trial** / **GARNET-like UK RWE (RWEQ) cohort (N[redacted]** / **GARNET-like UK RWE (RWEQ) - PLD monotherapy cohort (N=[redacted])**	Median OS for the GARNET-like UK RWE cohort is reported in Table 130 on page 290 of the appendices. Median PFS and OS for the GARNET-like UK RWE PLD monotherapy cohort were not provided to the ERG, but the	The ERG thanks the company for providing the information, which has been added to Table 11 of the revised ERG report.

		cohort (N=[redacted])
Median PFS (months) (95 % CI)	[redacted]	[redacted]
Median OS (months) (95% CI)	[redacted]	[redacted]

Median PFS (months) (95 % CI)	[redacted]	[redacted]
Median OS (months) (95% CI)	[redacted]	[redacted]

correct values are as reported here.

Issue 38 Incorrect information reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 13 on page 73 of the ERG report contains the following information regarding the comparator efficacy identified in the SLR, some of which is incorrect:	Please can the information be amended as follows:	As reported in Table 52 of the CS appendices, the therapy investigated in Makker *et al*. (2013) was doxorubicin monotherapy and the therapy investigated in Julius *et al*. (2013) was PLD.	The ERG has modified the text.

Comparator dataset	Nature	Comparator(s) included in the dataset
Makker et al. (2013)	Aggregated data from literature	Doxorubicin monotherapy & paclitaxel monotherapy
McMeekin et al. (2015)	Aggregated data from literature	Doxorubicin monotherapy &

Comparator dataset	Nature	Comparator(s) included in the dataset
Makker et al. (2013)	Aggregated data from literature	**Doxorubicin monotherapy**
McMeekin et al. (2015)	Aggregated data from literature	Doxorubicin monotherapy & paclitaxel monotherapy

		paclitaxel monotherapy		Julius et al. (2013)	Aggregated data from literature	**PLD**	
Julius et al. (2013)	Aggregated data from literature	Doxorubicin monotherapy					

Issue 39 Incorrect value reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Appendix 9.3.1, Page 217 The ERG report notes: *"At 20 years the waning adjusted ggamma model suggests about [redacted]% of patients are cured of endometrial cancer and will suffer the same mortality from other causes (other cancers, heart disease etc) as the matched general population."*	*"At 20 years the waning adjusted ggamma model suggests [redacted]% of patients are cured of endometrial cancer and will suffer the same mortality from other causes (other cancers, heart disease etc) as the matched general population."*	If the ERG is referring to the point at which the dostarlimab OS extrapolation is bounded by general population mortality, then this value should be [redacted]%, as reported in the CQ B8. Otherwise, please could the ERG provide further clarification about where the reported value of [redacted]% has been derived from.	The value has now been corrected to [redacted]%.

Issue 40 Incomplete presentation of ERG probabilistic results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6.1.2, Page 152 The ERG report notes: *The probabilistic model has an ICER of £113k per QALY with the*	Please could the ERG provide additional details about the methodology used for the probabilistic analyses reported in the ERG report, as well as a version of the model	The ERG currently do not present sufficient details on the probabilistic results presented in the report for these analyses to be reviewed or replicated.	No factual error. No revision required.

associated CEAC being presented in Figure 34. *The probabilities of dostarlimab being cost effective at the various NICE willingness to pay thresholds is presented in Table 52.* The ERG report includes the probabilistic results from the ERG's preferred assumptions; however, it is not clear how these have been derived from the ERG's version of the dostarlimab cost-effectiveness model.	where these probabilistic analyses are saved for review.		The probabilistic estimates were generated using the same ERG revised model as supplied to the company, with the values plotted being taken from PSA CALCS $BH$24:$BH$64

Issue 41 Typographical error (rounding)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 115 of the ERG report states "GARNET suggests that of those who have ceased dostarlimab treatment [redacted]% received a subsequent treatment"	Please can this be amended to: GARNET suggests that of those who have ceased dostarlimab treatment [redacted]% received a subsequent treatment.	The correct value is [redacted]% so this should be rounded up to [redacted]%.	The ERG has amended the text.

Issue 42 Typographical error (rounding)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 115 of the ERG report states "The RWEQ data suggests	Please can this be amended to:	The correct value is [redacted]% so this should be rounded up to [redacted]%.	The ERG has amended the text.

that after their 2nd line treatment [redacted]% of patients received a subsequent treatment"	The RWEQ data suggests that after their 2nd line treatment [redacted]% of patients received a subsequent treatment.		

Issue 43 Typographical error (rounding)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 115 of the ERG report states "The company adds an absolute 10% radiotherapy and 5% hormone therapy, resulting in a proportion receiving 3rd line treatment in the RWEQ arm of [redacted]%." Page 122 of the ERG report states "The company adds 10% radiotherapy and 5% hormone therapy to suggest a retreatment rate of [redacted]%."	Please can this be amended to: The company adds an absolute 10% radiotherapy and 5% hormone therapy, resulting in a proportion receiving 3rd line treatment in the RWEQ arm of [redacted]%. The company adds 10% radiotherapy and 5% hormone therapy to suggest a retreatment rate of [redacted]%.	The correct value is [redacted]% so this should be rounded up to [redacted]%.	The ERG has amended the text.

Issue 44 Incorrect value reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 30 on page 116 of the ERG report contains the following information regarding the cost of carboplatin plus gemcitabine, which is incorrect:	Please can the information be amended as follows:	As reported in Table 67 on page 165 of the CS, the cost per cycle of carboplatin plus gemcitabine is £66.12.	The ERG has corrected Table 30.

	Drug
Carboplatin + gemcitabine	£41

	Drug
Carboplatin + gemcitabine	£**66**

Issue 45 Incorrect value reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 30 on page 116 of the ERG report contains the following information, some of which is incorrect: DOST: £3,011 RWEQ: £2,881 Total Cost	Please can the value below in red be amended as follows: DOST: £3,011 RWEQ: £**2,883** Total Cost	As reported in Table 72 on page 174 of the CS, the correct value for the subsequent treatment costs for current clinical management is £2,883.12.	The ERG has corrected Table 30.

Issue 46 Typographical errors (rounding)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 37 on page 135 contains the following information across numerous rows, some of which is incorrect (note only the relevant rows with incorrect values are listed): Carb mono Age 65 - 75 years [redacted]	Please amend these values as follows: Carb mono Age 65 - 75 years [redacted]	The correct values are reported on Table 2 of the clarification questions. These values have been incorrectly rounded.	The ERG has amended the text.

	Carb+Pac				Carb+Pac		
ECOG at registry diagnosis				ECOG at registry diagnosis			
Unknown	[redacted]			Unknown	[redacted]		
Known	[redacted]			Known	[redacted]		
	Pac mono				Pac mono		
Histology at diagnosis				Histology at diagnosis			
Mixed carc.	[redacted]			Mixed carc.	[redacted]		
Non-spec. carc.	[redacted]			Non-spec. carc.	[redacted]		
	PLD mono	Carb mono			PLD mono	Carb mono	
Histology at diagnosis				Histology at diagnosis			
III	[redacted]	[redacted]		III	[redacted]	[redacted]	

Issue 47 Incorrect reporting of results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.3.3, Page 129 The ERG report notes "[redacted]".	[redacted]".	The reported number of respondents who answered yes and no are the wrong way around.	The ERG has amended 4.3.3.3. accordingly.

Issue 48 Unclear reporting of results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the ERG report (e.g. Table 2, page 17, Table 40 on page 144, Table 44 on page 147, Table 51 on page 151) it is not made clear that the reported life years (LY) are undiscounted, whereas costs and QALYs are discounted.	Please could it be made clear (e.g. with a footnote) that the LYs presented are undiscounted. Please update this throughout the ERG report.	LYs have been presented as undiscounted, whereas costs and QALYs are discounted. This should be made clear in the presentation of results throughout the report	The ERG has clarified this.

Issue 49 Incorrect section referenced

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr><td>Table 48 on page 150 of the ERG report references ‘Martin section’ as below:
<table>
<tr><th>Preferred assumption</th><th>Section</th><th>ICER</th></tr>
<tr><td>Company base-case</td><td>Error! Reference source not found.</td><td>£50,221</td></tr>
</table>
</td><td>Please can this be amended to reference the correct sections.</td><td>‘Martin section’ is not a section of the ERG report.</td><td>The redundant texts have been deleted.</td></tr>
</table>

ERG corrected company base-case	**Error! Reference source not found.**	£68,376			
ERG01: Dostarlimab OS Weibull	**Martin section Error! Reference source not found. Error! Reference source not found.**	£91,356			
ERG02: Dostarlimab ERG ITT TTD GGAM	**Martin section Error! Reference source not found.**	£73,101			

Issue 50 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Appendix 9.4.1, Page 227 *The ERG report notes "M=129"*	Please could this be corrected to state "**N**=129"	This section contains a typo.	Amended.

Issue 51 Unclear reporting of results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 25 on page 113 of the ERG report includes information on the Company quality of life models (Model 1 and Model 2). It is currently not made clear that Model 1 includes the time to death variable and Model 2 is a scenario excluding this.	Please could it be made clearer (e.g. with a footnote) that Model 1 includes a time to death variable and Model 2 is a scenario excluding this.	Model 1 includes a time to death variable, whilst model 2 excludes this. This is reported in the text on page 112 of the ERG report above Table 25, but is currently unclear in Table 25. Please could more detail be added for clarity.	The ERG has highlighted this in the text, though it can be noted that table 25 has n.a. for this variable for Model 2.

Issue 52 Inaccurate statement regarding quality of life analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 122 of the ERG report states "It is unclear whether the mean baseline quality of life value relates to the N=[redacted] or the N=[redacted]. This issue can be resolved at technical engagement by a	Please can this be amended to: **The mean baseline quality of life value relates to the N=[redacted] population.** ~~**This issue can be resolved at technical**~~	As reported on page 71 of the CS, data relating to patient responses to each of the EQ-5D-5L subscales are presented in Appendix N.3 of the CS. In Appendix N.3 of the CS, it is clear that for the	The ERG has amended the text to: "The mean baseline quality of life value relates to the N=[redacted] and not the N=[redacted]. The ERG

presentation of both values and their standard errors.”	~~engagement by a presentation of both values and their standard errors.~~	quality of life values, N=[redacted]. Therefore, the mean baseline quality of life value relates to N=86. N=[redacted] relates to the number of patients who had either EQ-5D-5L values for either baseline or post-baseline, but not both. Please can the ERG report be amended to reflect this.	thinks that the company should supply the mean quality of life value for the N=[redacted] as well, as there may be an issue around which is the most appropriate to use for the calculation of the quality of life values within the model. This issue can be resolved at technical engagement by a presentation of both values and their standard errors.”

Issue 53 Inaccurate statement regarding the exploration of alternative curves

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 146 of the ERG report states *“The ERG also highlights that the company restricts it exploration of the alternative functional forms of dostarlimab OS to the log logistic, log normal and generalised gamma.”*	Please can this sentence be removed from the ERG report: ~~“The ERG also highlights that the company restricts it exploration of the alternative functional forms of dostarlimab OS to the log logistic, log normal and generalised gamma.”~~	The Company explored alternative parametric curves for dostarlimab OS, which were all included within the economic model for the ERG to review and presented in Section B.3.3.4 to Section B.3.3.6 of the CS. For simplicity, the Company presented a selection of the curves as scenarios. Therefore, it is inaccurate to state that the Company restricted its exploration of alternative curve choices. Please can the ERG report be amended to reflect this.	No factual error. No revision required.

Issue 54 Inaccurate speculation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 237 of the ERG report states *"It appears that the company believe the flat tail starts at about* [redacted] *and should be ignored."*	Please can this sentence be removed from the ERG report: ~~**"It appears that the company believe the flat tail starts at about** [redacted] **and should be ignored."**~~	This is speculation and not based on evidence so please can this sentence be removed from the ERG report.	Text changed **from** "*"It appears that the company believe the flat tail starts at about* [redacted] *and should be ignored."* ***to*** *"The illustrative data shown to clinicians departs from the ToT KM at about* [redacted] *"*

Issue 55 Incorrect values reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 122 and 123 of the ERG provide a discussion of the calculation of the number needed to test (NNT). The report states *"If all patients need to be tested the NNT rises to 443% and the average testing cost to £930.* *The £250 cost per test is taken from NICE DG42, IHC screening for Lynch syndrome in people with endometrial cancer".*	Please can this be amended to: If all patients need to be tested the NNT rises to 443% and the average testing cost to £**929**. The £**210** cost per test is taken from NICE DG42, IHC screening for Lynch syndrome in people with endometrial cancer.	If all patients need to be tested, the average testing cost would be calculated as £210÷22.6×100 which equals £929.2. As reported in Table 74 on page 175 of the CS, and in NICE DG42, the cost per test is £210.	The ERG has revised its text accordingly.

SECTION 3: CONFIDENTIALITY HIGHLIGHTING AMENDMENTS

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EGR response</th></tr>
<tr><td>Pages 46–48, 51, 57 (Table 10), 65 (Table 11), 70 (Table 12), 86 (Table 16), 92</td><td>The number of patients in the GARNET ITT population (n=129) does not need to be marked as AIC. It was not marked as AIC in the CS as it is publicly available.</td><td>Please remove AIC highlighting on the GARNET ITT population (n=129).

Please can this be checked throughout the ERG report.</td><td>Amended.</td></tr>
<tr><td>Page 48</td><td>The median PFS estimate from GARNET should be marked as AIC as this has not been published.</td><td>Please amend the highlighting as follows:

“Median PFS estimate of [redacted] (from non-rounded up individual patient PFS estimates) informed the economic evaluation”.</td><td>Amended.</td></tr>
<tr><td>Table 11, page 67</td><td>The median PFS 95% CI values for ZoptEC should be marked as AIC as they have not been published.</td><td>Please can the 95% CI for ZoptEC be marked as AIC as follows:

<table><tr><th>Trial</th><th>ZoptEC (N=255)</th></tr><tr><td>Median PFS (months) (95 % CI)</td><td>4.7 ([redacted])</td></tr></table></td><td>Amended.</td></tr>
<tr><td>Page 75</td><td>The proportions of patients with endometrioid disease in GARNET and RWEQ should be marked as AIC.</td><td>Please can the proportions of patients with endometrioid disease be marked as AIC, as follows:

“The major differences in patient characteristics between GARNET and RWEQ as described in Section Error! Reference source not found. and Error! Reference source not found. (e.g. a much higher proportion of patients with endometrioid disease in GARNET, [redacted]% vs RWEQ, [redacted]%)”</td><td>Amended.</td></tr>
</table>

<table>
<tr>
<td>Page 112</td>
<td>No HRQoL data from GARNET has been published so the number of GARNET patients' EQ-5D-5L data being analysed should be marked as AIC.</td>
<td>Please can the confidentiality highlighting be amended as follows:
"The company analyses the GARNET EQ-5D-5L data of the ■ patients reporting their baseline EQ-5D and at least one subsequent EQ-5D"</td>
<td>Amended.</td>
</tr>
<tr>
<td>Table 30, page 116</td>
<td>The subsequent treatment costs for radiotherapy and hormone therapy in the model do not need to be marked as AIC as these are from the literature.</td>
<td>Please remove the AIC highlighting for radiotherapy and hormone therapy as follows:
<table>
<tr><th></th><th colspan="2">Model cycles</th></tr>
<tr><th></th><th>2nd line</th><th>3rd line</th></tr>
<tr><td>Radiotherapy</td><td>8.7</td><td>8.7</td></tr>
<tr><td>Hormone therapy</td><td>4.6</td><td>4.6</td></tr>
</table>
</td>
<td>Amended.</td>
</tr>
<tr>
<td>Table 31, page 117</td>
<td>The adverse events for the GARNET-like RWE cohort do not need to be marked as AIC as these are taken from the literature.
The total cost for AEs for dostarlimab should be marked as AIC as this could reveal the incidence of AEs from GARNET which have not been published.</td>
<td>Please amend the AIC highlighting as follows:
<table>
<tr><th></th><th>RWEQ</th><th>Cost</th></tr>
<tr><td>Abdominal pain</td><td></td><td>£375.46</td></tr>
<tr><td>Allergic reactions</td><td>3%</td><td>£404.26</td></tr>
<tr><td>Fatigue</td><td>4%</td><td>£0.00</td></tr>
<tr><td>Anaemia</td><td>4%</td><td>£485.28</td></tr>
<tr><td>Neutropenia</td><td>25%</td><td>£431.19</td></tr>
<tr><td>Thrombocytopenia</td><td>5%</td><td>£655.62</td></tr>
<tr><td>Nausea</td><td>1%</td><td>£447.58</td></tr>
<tr><td>Vomiting</td><td>1%</td><td>£447.58</td></tr>
<tr><td>Leukopenia</td><td>1%</td><td>£431.19</td></tr>
<tr><td>Sensory neuropathy</td><td>2%</td><td>£351.03</td></tr>
<tr><td>Hand and foot syndrome</td><td>3%</td><td>£404.26</td></tr>
</table>
</td>
<td>Amended.</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td><table>
<tr><td>Mucosal inflammation</td><td>1%</td><td>£391.93</td></tr>
<tr><td>Stomatitis</td><td>1%</td><td>£391.93</td></tr>
<tr><td>Dostarlimab total</td><td></td><td>[redacted]</td></tr>
<tr><td>RWEQ total</td><td></td><td>£214.93</td></tr>
</table></td><td></td></tr>
<tr><td>Table 42, page 145</td><td>The hazard ratios (HRs) derived from the MAICs have not been published so should be marked as AIC.</td><td>Please amend the confidentiality highlighting, by marking all HRs as AIC, as follows:
PFS HR [redacted] Makker, OS [redacted] HR Zoptec
PFS HR [redacted] Makker, OS [redacted] HR McMeekin
PFS HR [redacted] Makker, OS [redacted] HR Makker
PFS HR [redacted] Makker, OS [redacted] HR Julius
Individual treatment comparator: Paclitaxel monotherapy
PFS HR [redacted] Makker, OS [redacted] HR McMeekin
Individual treatment comparator: Carboplatin + paclitaxel
PFS HR [redacted] and OS [redacted] Rubenstein
PFS HR [redacted] and OS [redacted] Mazgani</td><td>Amended.</td></tr>
<tr><td>Page 122</td><td>The proportion of patients receiving radiotherapy and hormone therapy as subsequent treatments does not need to be marked as AIC.</td><td>Please remove the AIC marking for radiotherapy and hormone therapy as follows:
“The company adds 10% radiotherapy and 5% hormone therapy to suggest a retreatment rate of [redacted]%.”</td><td>Amended.</td></tr>
<tr><td>Page 13, 75, 228</td><td>The number of patients in the UK RWE GARNET like cohort (N=[redacted]) should be marked as AIC throughout the report.</td><td>N=[redacted]</td><td>Amended.</td></tr>
</table>

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **16 September**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.

- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**GlaxoSmithKline**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

[redacted]

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: The patient population specified in marketing authorisation and addressed in the Company submission (CS) is narrower that what is specified in the final scope	No	**The Company agrees that the patient population addressed in the Company submission is narrower than the patient population specified in the NICE final scope and that no further evidence or analyses are required.** The patient population addressed aligns with the marketing authorisation for dostarlimab, the patient population included in the GARNET trial, and the patient population who are anticipated to be eligible for treatment with dostarlimab in UK clinical practice, i.e. *adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen*.[1]
Key issue 2: Patients with advanced disease and with recurrent disease are potentially two distinct populations, but they were identified in different ways	No	**The Company disagrees with the ERG that patients with advanced disease and patients with recurrent disease represent two potentially distinct populations. Clinical expert feedback strongly indicates that both populations are treated the same in clinical practice and both populations face a lack of effective treatment options. The key points are as follows:** • **Both groups of patients fall into the post-platinum chemotherapy setting where they are considered to have incurable disease.** • **Prior NICE appraisals have appraised recurrent and advanced populations together**

between the GARNET trial for dostarlimab and the GARNET-like Real World EQuivalent (RWEQ) cohort		**in a similar manner.** **Therefore, breakdown of these two subgroups (by definition or proportion or study source) is not considered relevant for decision making.** **Analysis by subgroup: advanced versus recurrent disease** The Company is unable to fulfil the request to provide subgroup data stratified by patients with advanced versus recurrent disease from the GARNET trial, due to the limitations of the trial design. The eligibility criterion for GARNET (CS Appendix N, Table 96) required "proven recurrent or advanced solid tumour and disease progression after treatment with available anticancer therapies". However, further distinction of disease status was not collected during enrolment for GARNET, and so it is not possible to retrospectively distinguish between patients with recurrent disease and patients with advanced disease. The ERG's proposed resolution is to assume that patients with FIGO stage III or IV represent those patients with advanced disease, with all other patients assumed to have recurrent disease. This assumption would represent a substantial over-simplification, and would result in the incorrect classification of patients, given the limitations associated with the GARNET trial data collection, and the nature of staging in EC. Moreover, recurrent and advanced disease are not mutually exclusive disease states, and it could well be that patients with FIGO III/IV at diagnosis were initially treated with curative intent and subsequently experienced a recurrence and would fall under both categories. The Company disagrees with the ERG that patients with advanced disease and patients with recurrent disease represent two potentially distinct populations. Feedback from UK clinical experts has been unanimous that once patients have progressed following platinum-based chemotherapy, both patients with advanced disease and patients with recurrent disease are treated in the same way in clinical practice. All of these patients are considered to have incurable disease post-progression on platinum-based chemotherapy and the unmet need for an effective treatment option remains equally high in both populations. Further breakdown of these two subgroups is therefore

		not considered relevant to this appraisal and should not impact decision-making. The Company believes that the most robust approach is to analyse the full ITT population from the GARNET trial, in order to preserve the sample size of the study and to present clinical effectiveness evidence for the entire patient population for which dostarlimab is anticipated to represent a treatment option in UK clinical practice: patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy. A systematic review of all NICE appraisals of oncology indications published in the last 3 years identified 3 appraisals in a recurrent or advanced population, of which all 3 considered patients with recurrent or advanced disease as one combined population, with recommendations made for treatments across such a combined population, and separate subgroup data were not provided in all appraisals.[2-4] A non-systematic review of older appraisals also identified additional examples where this has been the case.[5, 6] These include: • TA707 (nivolumab as a treatment for previously treated unresectable advanced or recurrent oesophageal cancer)[2] • TA661 (pembrolizumab as a treatment option for patients with untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma)[3] • TA650 (pembrolizumab with axitinib for untreated advanced renal cell carcinoma)[4] • TA473 (cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck)[5] • TA347 (nintedanib in combination with docetaxel as a treatment option for patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma histology that has progressed after first line chemotherapy)[6] This past precedent should indicate to the Committee that the appraisal of both populations

		together should not be considered a major source of uncertainty in this appraisal. **Alignment of estimated incidence of recurrent disease reported in the RWEQ and Cancer Research UK data** In response to the ERG's concerns around the comparability of the GARNET and RWEQ populations with respect to the definition of patients with advanced versus recurrent disease, it is initially important to reiterate the Company's response to Clarification Question A16. The Company's response outlines the alignment between the estimated number of patients identified with recurrent disease in the RWEQ and the estimated incidence of recurrent disease according to the published literature.[7, 8] In the RWEQ, [redacted] patients were identified with recurrent disease over a six-year period. The published literature indicates that approximately 13% of patients with Stage I/II EC will subsequently experience disease recurrence.[7, 8] Based on the prevalence of EC from Cancer Research UK, this would result in an estimated 4,428 patients with Stage I/II disease who subsequently experienced disease recurrence over this six-year period and therefore provides close alignment to the estimated value based on the RWEQ. The Company also provided a sensitivity analysis as part of the response to Clarification Question A16, Table 13, showing that amending the definition of recurrence from 90 to 180 days had only a minimal impact on the number of patients identified (~[redacted]%). The Company therefore believe that this addresses the ERG's concerns regarding the definition of recurrence in the RWEQ.
Key issue 3: Overall the GARNET trial data were fairly immature and may	No	**The Company believes that the evidence presented in this appraisal is associated with sufficient levels of certainty to be considered for routine commissioning, for the reasons outlined throughout this response.** The Company acknowledges that the data from GARNET are not fully mature but believes that the

not be sufficient to provide reliable effectiveness and cost-effectiveness estimates		evidence presented in this appraisal is associated with sufficient levels of certainty to be considered for routine commissioning. It is noted that planned future data analysis from the GARNET trial will not be available during the timeframe of this appraisal.
Key issue 4: There are uncertainties over the magnitude of the benefit of dostarlimab relative to comparators due to the single-arm design of the GARNET trial and lack of suitable data for comparator treatments	No	**The Company recognise the limitations associated with the single-arm design of the GARNET trial and have made substantial efforts to identify different sources of comparative efficacy evidence. En masse, these provide sufficiently robust evidence for decision-making regarding the magnitude of benefit of dostarlimab relative to comparators.** The Company confirms that at this time there is no plan to undertake a randomised controlled trial of dostarlimab in this indication. This is due to a number of reasons that render the development of a Phase III randomised controlled trial in this indication challenging. Given the small target population, the feasibility of a randomised controlled trial with sufficient sample size is poor; indeed in some countries the target population (patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen) would meet local rare disease criteria. Moreover, the identification of an accurate comparator arm in this indication is particularly challenging, given the lack of established standard of care, which has been highlighted throughout the CS. Given the limitations associated with the single-arm design of the GARNET trial, the Company has made substantial efforts to identify different sources of comparative efficacy evidence to support this appraisal. While the analyses of these comparative efficacy sources are inherently associated with some uncertainty, the Company believes that these analyses en masse provide sufficiently robust evidence for decision-making regarding the magnitude of benefit of dostarlimab relative to comparators.
Key issue 5: GARNET trial population and	Yes	**Whilst it is not possible to adjust for dMMR/MSI-H status between the GARNET and RWEQ populations, substantial effort has been made to adjust for endometrioid disease status, and a matching-adjusted indirect comparison (MAIC) has been conducted between the**

RWEQ cohort may have fundamental differences that cannot be easily adjusted statistically		**endometrioid cohorts of GARNET and the RWEQ. Together these analyses may help to indicate the upper bound of the Company's base case ICER.** The ERG outlined concerns regarding the comparability of the GARNET and RWEQ populations, including the proportions of patients with advanced versus recurrent disease, endometrioid histology, and dMMR status within the two populations. The Company has already provided its response to the ERG's concerns relating to advanced versus recurrent disease in Key Issue 2. This response to Key Issue 5 focusses on the ERG's requests relating to dMMR status and endometrioid histology, and includes the methodology and results of a MAIC that has been conducted between GARNET and the RWEQ for the subgroup of patients with endometrioid only disease (new evidence submitted post-Technical Engagement call with ERG and NICE). **Comparative efficacy for mismatch repair status is not available** As dostarlimab is a novel, innovative therapy that represents the first treatment to specifically target the dMMR/MSI-H biomarker in EC, it is an unavoidable limitation that historical data for patients with EC do not include details on dMMR/MSI-H status. It is therefore not possible to provide any comparative efficacy evidence specifically for patients with dMMR/MSI-H, given the paucity of relevant data for patients with this biomarker in the published literature. Patient biomarker status was not reported in any of the chemotherapy trials identified in the clinical systematic literature review (SLR), and it is also not available in the RWEQ. To mitigate the ERG's concerns relating to this point, a meta-analysis has been conducted by the Company on the prognostic value of MMR/MS testing in EC and the results of the analysis found that there is not enough evidence to reject the null hypothesis that MMR/MS status is not a significant factor for overall survival (OS) and progression-free survival (PFS) in patients treated for EC.[9] This helps to confirm that the OS benefit of dostarlimab compared with currently used chemotherapies cannot be wholly explained by patients' MMR/MS status.[9] In every effort to mitigate any concerns relating to this point, subgroup analyses based on endometrioid status are presented below. It is believed that endometrioid disease may be linked to dMMR/MSI-H status, and therefore by presenting efficacy results for the patients with endometrioid

		disease, we hope to address some of the uncertainty relating to dMMR/MSI-H status between GARNET and the RWEQ. **Subgroup analysis of patients with an endometrioid tumour** In response to the ERG's concerns regarding the proportions of patients with endometrioid histology in GARNET and the RWEQ, the Company have conducted a post-hoc analysis of patients with an endometrioid histology in both cohorts. The results should be interpreted with caution, particularly when also considering the sample size reduction across both cohorts. A summary of the subgroup analysis of patients with an endometrioid tumour in GARNET (N=[redacted]) and the RWEQ (N=[redacted]) is presented in this section, and full results are presented in Appendix 1. It should be noted that the endometrioid cohort from GARNET presented below is slightly larger than the endometrioid cohort requested by the ERG in Clarification Question A6. This is because in addition to the [redacted] patients in GARNET with a Type I endometrioid carcinoma, [redacted] patients were moved from the non-endometrioid cohort to the endometrioid cohort to ensure sufficient overlap in the categories between the GARNET and RWE cohorts for the MAIC analysis. These patients had a histology of endometrial adenocarcinoma (N=[redacted]), endometrioid adenocarcinoma (N=[redacted]), moderately differentiated endometrial adenocarcinoma with solid aspects (N=[redacted]) and adenocarcinoma (N=[redacted]). As most endometrial adenocarcinomas would be of endometrioid histology, these [redacted] patients were included in the endometrioid cohort from GARNET when aligning the categories between the two cohorts, resulting in a total subgroup size of N=[redacted]. ***Baseline characteristics*** A summary comparison of the baseline characteristics for the endometrioid cohort in GARNET (N=[redacted]) and the endometrioid cohort in the RWEQ (N=[redacted]) is presented in Table 1. Overall, the baseline characteristics of the two subgroups suggest that the patient populations appear to be reasonably well-matched. The most notable differences occurring across Eastern Cooperative Oncology Group Performance Status (ECOG PS), FIGO stage and grade may likely be the result of different timings of assessment between the GARNET and UK RWE studies, rather than true

imbalances between the two populations.

Table 1: Baseline characteristics for the endometrioid cohorts in GARNET and the RWEQ

Baseline characteristics	Dostarlimab (GARNET endometrioid cohort) (N=[redacted])	Current clinical management (RWEQ endometrioid cohort) (N=[redacted])
Race/ethnicity		
Black	[redacted]	[redacted]
Other Race	[redacted]	[redacted]
White	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Age category		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
<65 years	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]
ECOG performance status at index		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Histology at initial diagnosis		
Endometrioid	[redacted]	[redacted]
FIGO Stage at initial diagnosis		
Stage I	[redacted]	[redacted]
Stage II	[redacted]	[redacted]
Stage III	[redacted]	[redacted]

		Stage IV	[redacted]	[redacted]
		Disease grade at initial diagnosis		
		Grade 1/2	[redacted]	[redacted]
		Grade 3/4	[redacted]	[redacted]
		Unknown	[redacted]	[redacted]
		Number of prior platinum-based therapies in the advanced/recurrent setting		
		0[a]	[redacted]	[redacted]
		1	[redacted]	[redacted]
		2	[redacted]	[redacted]
		3[b]	[redacted]	[redacted]
		Surgery for advanced or recurrent endometrial cancer		
		Yes	[redacted]	[redacted]
		No	[redacted]	[redacted]

Footnotes: [a] One patient was recorded as having had 1 line of platinum-based therapy per the GARNET methodology, with a protocol deviation because an adequate duration of time was not present between the prior anticancer therapy and the first administration of dostarlimab. [b] One patient is recorded as having three lines of prior platinum-based chemotherapy, which included treatment in the neoadjuvant/adjuvant setting. The GARNET trial protocol stipulated that patients had to have received no more than 2 lines of anti-cancer therapy for recurrent or advanced (≥Stage IIIB) disease. Any treatment a patient received for early stage disease would not have fallen into this criterion.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; FIGO: Federation of Gynecology and Obstetrics; ITT: Intention to treat; RWE: real-world evidence; RWEQ: real-world equivalent; SD: standard deviation.

Results

A summary of PFS and OS results for patients in the endometrioid cohorts of GARNET and the RWEQ are presented in Table 2 and Table 3 alongside a comparison of the corresponding outcomes for the respective ITT populations. More detailed results, including Kaplan-Meier (KM) curves, are presented in Appendix 1.

Table 2: Naïve PFS comparison (RWEQ versus GARNET; ITT populations versus endometrioid cohorts)

	Dostarlimab (GARNET ITT population) (N=129)	Dostarlimab (GARNET endometrioid cohort) (N=[redacted])	Current clinical management (RWEQ GARNET-like cohort) (N=[redacted])	Current clinical management (RWEQ endometrioid cohort) (N=[redacted])
Median PFS (months) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PFS rates (95% CI)				
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: TTNT was used as a proxy for PFS in the RWEQ. Small differences in PFS rates versus the CS may be observed as exact rates were not available at the time of CS and were instead estimated from the KM curve.
Abbreviations: CI: confidence interval; ITT: intention-to-treat; NE: not estimable; PFS: progression-free survival; RWE: real-world evidence; RWEQ: real-world equivalent; TTNT: time to next treatment.

Table 3: Naïve OS comparison (RWEQ versus GARNET; ITT populations versus endometrioid cohorts)

	Dostarlimab (GARNET ITT population) (N=129)	Dostarlimab (GARNET endometrioid cohort) (N=[redacted])	Current clinical management (RWEQ GARNET-like cohort) (N=[redacted])	Current clinical management (RWE endometrioid cohort) (N=[redacted])
Median OS (months) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS rates (95% CI)				
Month 6	[redacted]	[redacted]	[redacted]	[redacted]

Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Small differences in OS rates versus the CS may be observed as exact rates were not available at the time of CS and were instead estimated from the KM curve.
Abbreviations: CI: confidence interval; ITT: intention-to-treat; NE: not estimable; OS: overall survival; RWE: real-world evidence; RWEQ: real-world equivalent.

Matching adjusted indirect comparison (MAIC) between the endometrioid cohorts of GARNET and the RWEQ

Methodology

In order to investigate the impact of the imbalances in baseline characteristics between the endometrioid cohorts in GARNET and the RWEQ, two MAICs were conducted as per the methodology detailed previously for the respective ITT populations in the CS Document B, Section B.2.7.1 and Appendix D.5.1. Matching-adjusted KM data were derived for both OS and PFS, but it was only considered appropriate to calculate hazard ratios (HRs) for OS, given the differences in the definitions of PFS between the two studies (PFS in GARNET versus time to next treatment [TTNT] in the RWEQ), as well as the associated timepoints of assessment.

The two MAIC scenarios considered are presented in Table 4. These are aligned with the two MAIC scenarios conducted in Document B, Table 23, except for the removal of histology as a matching variable from both scenarios as all patients in this subgroup analysis had endometrioid disease.

Table 4: Scenarios considered in the MAICs between the endometrioid cohorts of GARNET and the RWEQ

Scenarios	Prognostic variables
MAIC Scenario 1	• Number of prior platinum-based therapies in the advanced/recurrent setting[a]

MAIC Scenario 2	• Race/ethnicity • Stage at diagnosis • Prior surgery

[a] Patients with 0 or ≥2 prior platinum-based therapies from the GARNET cohort were removed in order to achieve balance.
Abbreviations: MAIC: matching-adjusted indirect comparison; RWEQ: real-world equivalent.

A summary of the MAIC results for OS in the endometrioid cohorts are presented in Table 5 below. Matching-adjusted KM curves for OS, PFS and time to treatment discontinuation (TTD) are presented in Appendix 1. The naive HR between dostarlimab and current clinical management in this cohort ([redacted]) was similar to the matching-adjusted HRs ([redacted] in both scenarios), suggesting that there were only minor imbalances between the two endometrioid cohorts in the naïve comparison which result in a slight underestimation of the treatment effect associated with dostarlimab.

Table 5: MAIC results for OS between GARNET (before and after matching) and the RWEQ (endometrioid cohorts)

	Current clinical management (RWEQ endometrioid cohort) (N=[redacted])	Dostarlimab (GARNET endometrioid cohort – prior to matching) (N=[redacted])	Dostarlimab (Matching-adjusted GARNET endometrioid cohort - MAIC Scenario 1)	Dostarlimab (Matching-adjusted GARNET endometrioid cohort - MAIC Scenario 2)
ESS	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS rate at 6 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS rate at 12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

		OS rate at 18 months (95% CI) [redacted]
		HR for OS (95% CI) for dostarlimab versus current clinical management [redacted]
		P value for hazard ratio [redacted]

Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; ITT: intention-to-treat; NA: not applicable; NE: not estimable; OS: overall survival; RWE: real-world evidence: MAIC: matching-adjusted indirect comparison.

Conclusions

Overall, it would appear reasonable to conclude that a naive comparison between the endometrioid cohorts in GARNET and the RWEQ provide a ceiling to the upper limit of uncertainty for the treatment effect between dostarlimab and current clinical management. The naive treatment effect observed in the endometroid subgroup analysis is likely to be conservative, given the outstanding imbalances between the two populations, including age (the RWEQ endometrioid cohort is younger than the GARNET endometrioid cohort), and prior treatments ([redacted]% of the GARNET endometrioid population received two or more prior treatments, compared to [redacted]% in the RWEQ endometrioid cohort), which likely introduce slight bias in favour of current clinical management.

It is also important to note that the endometrioid cohort only represents a portion of the total patient population eligible for dostarlimab in the UK, and consideration of the endometrioid subgroup only excludes a proportion of patients who face an equally high unmet need. Furthermore, as a *post-hoc* analysis, the results of these scenarios should be interpreted with caution, considering the sample size reduction across both cohorts, and the resulting increased uncertainty.

Cost-effectiveness results (endometrioid cohorts)

Given the similarities between the PFS and OS data for the endometrioid cohorts, and the corresponding cohorts for the GARNET ITT population and the full RWEQ population, the same curve choices were used to model PFS and OS for dostarlimab and current clinical management in

the endometrioid cohorts as the curves chosen in the base case cost-effectiveness analysis. Full details on the statistical fit associated with all of the parametric extrapolations, as well as the long-term survival estimates, are detailed in Appendix 1.

A summary of the endometrioid cohort scenario analyses is presented in [redacted]Table 6. The limitations with HR-based approaches (detailed below in Additional Issue 1) suggest that the true ICER for the comparison of the endometrioid cohorts in GARNET and the RWEQ may lie between £53,437 and £55,626. The Company believes that this range of ICERs therefore represents the upper limit of uncertainty associated with the base case cost-effectiveness analysis.

It should also be noted that the Company's MAICs versus RWE conducted in the original submission suggested that there were imbalances between the ITT GARNET and RWEQ populations that underestimated the true treatment benefit associated with dostarlimab. The Company has also explored fitting an independent extrapolation to the matching-adjusted GARNET ITT OS KM data from the previously presented MAIC versus the RWEQ, Scenario 1, which results in an ICER of £43,977 (Table 16).

The Company believes that, taken together, these results indicate that the base case cost-effectiveness analysis ICER of £48,608, lies between the lower limit of uncertainty from the RWE MAIC (£43,977), and the upper limit of uncertainty from the endometrioid scenarios (£53,437 and £55,626).

[redacted]Table 6: Scenario analyses based on endometrioid cohorts of GARNET and the RWEQ ([redacted]% PAS for dostarlimab)

Scenario analysis	Incr. costs	Incr. QALYs	ICER
Company Revised base case	[redacted]	[redacted]	£48,608
Scenario 3	[redacted]	[redacted]	£48,614

		• Dostarlimab PFS: Independent extrapolation of unmatched endometrioid GARNET KM data (Log-logistic) • RWEQ PFS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic) • Dostarlimab OS: Independent extrapolation of unmatched endometrioid GARNET KM data (Generalised gamma) • RWEQ OS: Matching-adjusted HR ([redacted]) applied to independently extrapolated endometrioid GARNET KM data – MAIC Scenario 1			
		Scenario 4 • Dostarlimab PFS: Independent extrapolation of unmatched endometrioid GARNET KM data (Log-logistic) • RWEQ PFS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic) • Dostarlimab OS: Independent extrapolation of matching-adjusted endometrioid GARNET KM data (Generalised gamma) – MAIC Scenario 1 • RWEQ OS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic)	[redacted]	[redacted]	£53,437
		Scenario 5 • Dostarlimab PFS: Independent extrapolation of unmatched endometrioid GARNET KM data (Log-logistic) • RWEQ PFS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic) • Dostarlimab OS: Independent extrapolation of unmatched endometrioid GARNET KM data (Generalised gamma) • RWEQ OS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic)	[redacted]	[redacted]	£55,626
		Abbreviations: HR: hazard ratio; Incr.: incremental; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; RWEQ: real-world equivalent; MAIC: matching-adjusted indirect comparison.			

		Comparison between dostarlimab and patients receiving carboplatin plus paclitaxel in the RWEQ As an alternative solution to Key Issue 5, the ERG previously proposed that a comparison between the GARNET ITT population and patients receiving carboplatin plus paclitaxel in the RWEQ could be used as a proxy for a fitter overall RWEQ cohort. However, the Company does not believe that this approach is appropriate to use as a proxy for a comparison versus the overall RWEQ population. The RWEQ carboplatin plus paclitaxel cohort may potentially be a fitter population of patients overall. However, the associated efficacy data would be confounded by the potentially increased efficacy of carboplatin plus paclitaxel, relative to the other relevant comparators that comprise the basket of current clinical management. Using the results of this comparison as a proxy for a comparison versus current clinical management would therefore be associated with bias and would not be appropriate for decision-making. **Grade** During the TE call, the ERG noted the effect of tumour grade on OS (grade 3/4 versus 1/2) was shown to be in opposite directions in separate Cox regression models for GARNET and the RWEQ in the RWE MAICs, resulting in a HR between grade 3/4 versus grade 1/2 of [redacted] (95% CI [redacted] to [redacted]) for the GARNET cohort compared to [redacted] (95% CI [redacted] to [redacted]) for the RWEQ cohort. However, it is important to highlight the wide confidence intervals from the GARNET trial here (from [redacted] to [redacted]), which mean that the point estimate for the GARNET cohort should be interpreted with caution and is subject to uncertainty.
Key issue 6: Model errors	No	**The Company has incorporated a revised version of the ERG's preferred treatment waning methodology into its base case cost-effectiveness analysis, alongside the majority of the ERG's preferred assumptions outlined in Issue 6. The Company has not included the costs associated with cisplatin plus doxorubicin and the subsequent treatment modifier for**

		dostarlimab. As a result of these changes the Company's revised base case ICER is £48,608. [redacted] **Treatment waning** The Company agrees that the ERG's treatment waning approach is more appropriate when considering individual extrapolations of KM data in both treatment arms. Nevertheless, the Company believe that both the treatment waning methodology employed in the original CS and the ERG's revised approach are oversimplified, because: • they assume that all patients have discontinued treatment with dostarlimab at Year 2 and • they assume that any patients who continue to receive treatment past 2 years do not receive any benefit from it. Therefore, the Company has incorporated a revised treatment waning methodology based on the ERG's approach but adapted it to account for patient treatment discontinuation. Further details of this revised methodology are provided in response to Key Issue 9. **Percentage of patients continuing to receive dostarlimab past the first cessation point** The Company acknowledges the ERG's correction of the percentage of patients who continue to receive dostarlimab beyond the first cessation point and has incorporated the ERG's approach in its updated cost-effectiveness analysis. This change results in a minimal impact on the original base case ICER. **Dostarlimab administration costs** The Company acknowledges that the ERG's suggested approach to modelling the cost of administration for dostarlimab is appropriate, and this has been incorporated into the revised cost-effectiveness analysis. This change results in a minimal impact on the original base case ICER. **Subsequent treatments** The Company acknowledges that the number of subsequent treatments received by patients

		following treatment with dostarlimab may be uncertain due to the short-term follow-up of the GARNET trial. Moreover, using a multiplier of 1.4 based on the GARNET data is highly uncertain given that GARNET was conducted globally, the paucity of information about subsequent treatments, and the very small sample size that this is based on. The lack of a comparator arm in GARNET means it is not possible to determine whether patients receiving current clinical management may also have received more than one subsequent treatment. Consequently, the Company disagrees with the ERG's inclusion of a subsequent treatment modifier of 1.4 to the dostarlimab arm only, because there is uncertainty about whether a subsequent treatment modifier could also exist for the comparator. As such, the Company believes it is more appropriate to assume no subsequent treatment modifiers, rather than applying a modifier to one arm only. **Inclusion of cisplatin plus doxorubicin** The Company disagrees with the ERG's preference to include the costs of cisplatin plus doxorubicin within the base case cost-effectiveness analysis, and believes it is misleading to denote this as a modelling error. Cisplatin plus doxorubicin was not included into the costing of the RWE basket as a result of the 5% threshold, which was chosen for a number of reasons. First, if the threshold is lowered, for example from 5% to 3%, the SACT data are likely to capture treatments which are used in the treatment of other cancers, such as ovarian or breast cancer, for patients with a multi tumour flag. Whilst it is acknowledged that the efficacy of these treatments is captured within the RWEQ basket, it would not be appropriate to include the costs of treatments that might not be used in endometrial cancer, and therefore the 5% threshold was maintained. Second, it is also important to note that where the ERG have included cisplatin plus doxorubicin within their base case analysis, the ERG have not included any AEs associated with cisplatin plus doxorubicin, or associated AE costs and disutilities. The results should therefore be interpreted

		with caution. **Submission utility values** The Company provided an updated set of utility values for the N=[redacted] subset of the GARNET trial in response to Clarification Question B2, and these utility values have been incorporated into the revised cost-effectiveness analyses presented throughout this response document. **Time to death utilities** The Company believes including a time to death variable to calculate utilities is the most appropriate approach. There is a growing body of evidence which highlights that a patient's HRQoL declines substantially in the weeks and months prior to death, and the inclusion of time to death utilities has been accepted in previous NICE appraisals.[10-12] Accordingly, the Company continues to use time to death utilities in its base case cost-effectiveness analysis.
Key issue 7: Dostarlimab overall survival (OS) elicitation exercise and choice of OS curve	No	**The Company believes that the Generalised gamma extrapolation represents the most appropriate OS curve choice but notes that this choice underestimates long-term dostarlimab OS compared to mean clinical expert estimates of survival, and therefore should be considered conservative. The ERG's preferred Weibull curve choice does not adequately suffice the three key criterion when selecting an appropriate parametric function; it provides the worst statistical fit to the GARNET OS KM data, there are concerns with regard to its clinical plausibility, and it substantially underestimates OS compared to the mean estimates of survival obtained by clinical experts.** **Limitations associated with the ERG's preferred Weibull curve choice to model OS for dostarlimab** The ERG's use of the Weibull curve to model OS for dostarlimab is associated with substantial limitations, because of the monotonic hazard profile associated with the Weibull curve, which assumes that patients receiving treatment with dostarlimab have an almost constant risk of death from initiation of treatment until they die, irrespective of whether they continue to receive treatment

during this time. The hazard profile of the Weibull curve used to model OS for dostarlimab for the GARNET ITT population is shown in Figure 1. This hazard profile is not reflective of clinical experience with immuno-oncology (I-O) therapies.

Figure 1: Dostarlimab OS hazards modelled by the Weibull curve

Abbreviations: OS: overall survival.

Typically, patients treated with an I-O therapy experience an initially increased hazard of death relative to chemotherapy, but then patients who respond to I-O therapy experience a decreased hazard of death relative to chemotherapy after receiving treatment for a certain duration of time. For example, the Final Appraisal Document of TA707 notes that *"At 2 and 4 months, people having nivolumab had worse overall survival than people having taxane. However, from 6 months*

		onwards, overall survival was higher for nivolumab compared with taxane. The clinical expert explained that this pattern in overall survival is commonly found with immunotherapies. This is because of the delay in benefit as the immune system is activated, whilst chemotherapy immediately acts on the cancer cells."[2] The above pattern, commonly observed with I-O therapies, is not consistent with the ERG's preferred Weibull curve. Notably, many of the other parametric extrapolations considered in the CS represent non-monotonic hazard shapes, which are considered to more plausibly represent the typical hazard profile associated with an I-O therapy. For example, in TA707, the Company preferred the non-monotonic log-logistic extrapolation to model nivolumab OS, while the ERG preferred the Generalised gamma extrapolation.[2] The hazard profiles associated with all of the dostarlimab parametric extrapolations considered in the CS are presented in Figure 2 (over 5 years) and Figure 3 (over 40 years). **Figure 2: Dostarlimab OS hazards over five years**

		 **Abbreviations:** OS: overall survival. **Figure 3: Dostarlimab OS hazards over 40 years**

		 **Abbreviations:** OS: overall survival. Except for the exponential, Weibull and Gamma distributions, all of the extrapolations presented above represent non-monotonic hazard functions, which are much more representative of the typical mechanism of action of an I-O therapy. In comparison, the constant hazards modelled by the Weibull, exponential and Gamma distributions do not adequately represent the hazard profile associated with an I-O therapy, and the Company therefore believes these extrapolations should be excluded from consideration. The concerns associated with the Weibull curve are further pronounced when it is modelled alongside the log-logistic curve used to extrapolate OS for current clinical management based on the RWEQ. A comparison between the hazards of death for dostarlimab (Weibull) versus current

		clinical management (log-logistic) are presented in Figure 4. **Figure 4: OS hazards for dostarlimab (Weibull) versus current clinical management (log-logistic)**  **Abbreviations:** OS: overall survival. The Company asks the ERG to provide an evidence-based rationale to suggest that the hazard profile modelled by the Weibull extrapolation is clinically plausible, in line with the NICE TSD 14 recommendation: "*While fitting separate parametric models to individual treatment arms may be justified, it is important to note that fitting different types of parametric model (for example a Weibull for one treatment arm and a log normal for the other) to different treatment arms would require substantial justification, as different models allow very different shaped distributions. Hence if the*

		proportional hazards (PH) assumption does not seem appropriate it is likely to be most sensible to fit separate parametric models of the same type, allowing a two-dimensional treatment effect on both the shape and scale parameters if the parametric distribution".[13] When the two curves are compared, the ERG's preferred base case analysis assumes that after approximately 5 years, patients who initially received treatment with dostarlimab are at a higher risk of death compared to patients treated with chemotherapy. Patients treated with dostarlimab then continue to experience an increased risk of death for the remainder of the model time horizon. The Company does not believe that there is any evidence or clinical rationale to support this assumption, and when considering the clear evidence of an OS benefit associated with dostarlimab – based on both naïve and matching-adjusted comparisons between GARNET and the RWEQ – as well as the potential for long-term responses in patients who receive I-O therapy, the Company believes that this assumption is inappropriate. During the technical engagement call between NICE, the ERG and the Company, the ERG noted that they did not believe that this clinical implausibility (hazard curve shape) was a concern, because the dostarlimab hazard was only applied for [redacted], before treatment waning was applied, meaning that the dostarlimab OS curve is only partially used following this point, and is not used at all after [redacted]. The Company believes that in itself, this is an extremely pessimistic assumption which is discussed further in Key Issue 9, alongside the Company's proposed revised treatment waning approach. With regard to treatment waning, it should be noted that the application of treatment waning in the ERG's base case causes the 'waned' dostarlimab OS curve to increase once treatment waning is applied, compared to the OS curve before treatment waning (Figure 5). This assumption is not clinically plausible. **Figure 5: Comparison of the Weibull extrapolation for dostarlimab OS before and after treatment waning**

		 **Abbreviations**: OS: overall survival. It is important to note that the Weibull curve is associated with either the worst, or joint worst, statistical fit to the dostarlimab OS KM data out of all of the parametric functions considered in the CS, Document B (Table 55), raising further concerns about the appropriateness of this curve choice. The ERG's argument that the dostarlimab OS curve is only used in full for the first two years underlines the importance of choosing an OS curve which provides a good statistical fit to the observed OS KM data. Finally, it is important to note that the Weibull substantially underestimates OS compared to the mean clinical expert estimates of survival presented in the CS Document B, and outlined below in Table 7.

		Choice of Generalised gamma curve for dostarlimab OS It should be noted that, using the Company's preferred treatment waning methodology (Key Issue 9), all of the dostarlimab extrapolations result in broadly similar long-term survival predictions, unlike in the original base case cost-effectiveness analysis presented in the CS. These post-treatment waning extrapolations are presented below – minor differences are observed over the first five to ten years, but the curves then converge and follow a similar trajectory for the remainder of the model time horizon (Figure 6, Figure 7). **Figure 6: Dostarlimab OS extrapolations up to 5 years (GARNET ITT population) (post-treatment waning, in line with the methodology detailed in Key Issue 9)**  **Abbreviations:** ITT: intention-to-treat; OS: overall survival. **Figure 7: Dostarlimab OS extrapolations up to 40 years (GARNET ITT population) (post-treatment waning, in line with the methodology detailed in Key Issue 9)**

Abbreviations: ITT: intention-to-treat; OS: overall survival.

The Company believes that the revised treatment waning methodology should mitigate the ERG's concerns that the dostarlimab Generalised gamma extrapolation of OS generates implausible survival estimates. All of the post-treatment waning dostarlimab curves could be considered pessimistic, and underestimate OS when compared to the mean clinician estimates of survival (Table 7).

Table 7: Proportion of patients predicted to be alive at each time point following treatment with dostarlimab for each parametric extrapolation (post-treatment waning) compared to the mean clinical expert estimates

	Proportion of patients predicted to be alive at each time point following treatment with dostarlimab, %				
Time	Generalised Gamma	Log-logistic	Log-normal	Weibull	Mean clinical expert estimates

		3 years [redacted] 5 years [redacted] 10 years [redacted] 15 years [redacted] 20 years [redacted] Based on Table 7, the Generalised gamma curve appears to be the most clinically plausible choice, predicting survival estimates that are most closely aligned with the mean clinical expert estimates at 5, 10, 15 and 20 years respectively, and as such, the Company maintain that the Generalised gamma curve is still the most appropriate curve choice for dostarlimab OS. **Appropriateness of Survival Estimates** In response to the ERG's concerns regarding the expert elicitation process, the Company would like to add that the survival probabilities presented to clinical experts during the elicitation exercise, and subsequently used in the Company's treatment waning adjusted curve selection, were from GARNET KM data. Since KM data are non-parametric data, the Company disagrees with the ERG and underlines that using non-parametric data should not be considered wrong to justify adjusted curve choices, which are parametric data. It should also be noted that, whilst the exact starting point and duration of treatment waning were not specifically given to clinicians, it is reasonable to assume that the clinicians would have made their own assumptions about the timepoint at which most patients would have discontinued treatment with dostarlimab, and would have made their own assumptions about a plausible duration of lasting treatment effect following this, based on their own experience of current clinical practice. It is therefore appropriate to use these survival estimates to select the most clinically plausible dostarlimab OS curve, post-treatment waning. The Company is not clear on how the ERG's preferred approach, to choose an OS curve before treatment waning, could be more appropriate. Choosing an OS curve prior to treatment waning will mean that the modelled OS curve

		following treatment waning is guaranteed to be different to the clinical experts' survival predictions. **Proportion of life years (LYs) gained in the PFS versus PPS health states** The ERG highlighted concerns that the Company base case anticipates two thirds of survival in the dostarlimab arm will occur after progression, with around three quarters of the net quality-adjusted life year (QALY) gain also occurring after progression. Firstly, the Company believes it is reasonable to assume that patients treated with dostarlimab would experience improved LYs and QALYs in the post-progression state compared to current clinical management, for a number of reasons. These include: • A higher proportion of patients treated with dostarlimab may subsequently receive platinum-based doublet chemotherapies compared to patients treated with current clinical management. In the base case cost-effectiveness analysis, [redacted]% of patients received platinum-based doublet chemotherapy following dostarlimab, versus [redacted]% of patients following current clinical management, based on data from the RWEQ. Doublet chemotherapies are typically associated with higher efficacy than monotherapies, for example, as highlighted in Key Issue 12. • The improved PFS associated with dostarlimab versus current clinical management means that patients treated with dostarlimab experience a substantial delay between their prior platinum-based chemotherapy, and any future chemotherapy regimens, providing them respite from the side effects and debilitating toxicity associated with chemotherapy. In the Company's base case cost-effectiveness analysis, patients receiving dostarlimab spend a mean [redacted] years in the progression-free state, compared to [redacted] years for patients receiving current clinical management. This may mean that patients are fitter, and better able to tolerate their subsequent chemotherapy following dostarlimab, compared to current clinical management, which may allow them to remain on treatment longer, or to tolerate doublet chemotherapy instead of monotherapy, both of which it is reasonable to assume would be associated with improved LYs and QALYs for dostarlimab versus current clinical management in the post-progression setting.

- Published evidence indicates that other I-O therapies are associated with post-progression survival gains.[14-16]

The ERG's interpretation of the Company's base case, and the disproportionate LY/QALY gain in the PPS state, means that the dostarlimab OS curve is overestimated. The Company believes that, instead, the dostarlimab PFS curve is underestimated – the lognormal PFS curve for dostarlimab used in the base case cost-effectiveness analysis is substantially lower than the clinical expert estimated PFS at all timepoints (Table 8). The Company believes this underestimation contributes to in the disproportionate LY/QALY gain in the post-progression health state.

The ERG noted concerns that outlier clinical expert estimates of survival meant that the mean estimates from all the clinicians were associated with uncertainty and may be overestimated. As such, the Company has conducted an exploratory analysis, which calculated the mean clinical expert estimates of PFS, excluding the two highest clinical expert estimates at each timepoint as outliers. Table 8 below shows that the lognormal extrapolation used for PFS in the Company's base case cost-effectiveness analysis still substantially underestimates PFS compared to these conservative mean clinical expert estimates (Table 8).

Table 8: Comparison of long-term PFS estimates for dostarlimab from modelled extrapolations and clinical experts

Time	Estimated proportions of patients who are progression-free (Dostarlimab KM data), %	Estimated PFS % (Lognormal extrapolation as per Company base case), %	Mean clinical expert estimates (PFS), %	Mean clinical expert estimates (PFS, excluding two highest estimates), %
Year 2	[redacted]	[redacted]	[redacted]	[redacted]
Year 2.5	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]	[redacted]

Year 10	[redacted]	[redacted]	[redacted]	[redacted]	
Year 15	[redacted]	[redacted]	[redacted]	[redacted]	
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: OS: overall survival; PFS: progression-free survival; KM: Kaplan-Meier; NA: not applicable; NR: not reported.

To investigate the impact that the potential underestimation of PFS has on the proportion of LYs and QALYs gained pre- and post-progression, the disaggregated LYs and QALYs from the Company's base case cost-effectiveness analysis are presented in Table 9 and Table 10, alongside the equivalent results when PFS extrapolation based on the Generalised gamma is used for dostarlimab.

With the lognormal extrapolation, [redacted]% and [redacted]% of the total LYs and QALYs gained for patients treated with dostarlimab are gained post-progression. However, if the Generalised gamma is used to model PFS for dostarlimab instead, then only [redacted]% and [redacted]% of the total LYs and QALYs gained are accrued post-progression. Given that the Generalised gamma curve still underestimates PFS compared to the conservative mean clinical expert estimates, the disproportionate LY/QALYs gained post-progression are likely the result of the dostarlimab PFS curve being underestimated in the Company base case cost-effectiveness analysis.

Table 9: Disaggregated LYs by health state for dostarlimab and current clinical management using either the lognormal or Generalised gamma extrapolations for dostarlimab PFS

Health state[a]	Total LYs Dostarlimab PFS (lognormal)		LYs gained	Total LYs Dostarlimab PFS (Generalised gamma)		LYs gained
	Dostarlimab	Current clinical management		Dostarlimab	Current Clinical Management	
PFS, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		PD, % [redacted] **Total** [redacted] [a] Discounted LYs. **Abbreviations**: LY: life year; PD: progressed disease; PFS: progression-free survival. **Table 10: Disaggregated QALYs by health state for dostarlimab and current clinical management using either the lognormal or Generalised gamma extrapolations for dostarlimab PFS** **Costs by health state[a]** / **Total QALYs Dostarlimab PFS (Lognormal)** — **Dostarlimab** / **Current clinical management** / **QALYs gained** / **Total QALYs Dostarlimab PFS (Generalised gamma)** — **Dostarlimab** / **Current clinical management** / **QALYs gained** **PFS** [redacted] **PD** [redacted] **AE disutilities** [redacted] **Total** [redacted] [a] Discounted QALYs. **Abbreviations**: AE: adverse event; PD: progressed disease; PFS: progression-free survival; QALY: quality-adjusted life year.
Key issue 8: RWEQ OS elicitation exercise and choice of OS curve	Yes	**The Company's preferred log-logistic extrapolation for RWEQ OS represents the best statistically fitting curve, as well as the most optimistic curve with regard to the predicted long-term survival estimates for current clinical management. There are no plausible alternative approaches that could be used to fit a parametric extrapolation to the RWEQ OS data.** **Choice of current clinical management OS curve**

The Company does not believe the ERG's concerns regarding the choice of OS curve for the RWEQ are justified. The data for the RWEQ were derived from a patient population of N=[redacted] over a period of seven years of follow-up, meaning that the RWE KM data should be considered less uncertain than the KM data from GARNET.

The Company believes that the most appropriate curve selection for current clinical management OS is the log-logistic curve (Section B.3.3.6 of the CS). The log-logistic curve represents the best statistical fit, as well as the most optimistic curve with regard to the predicted long-term survival estimates associated with current clinical management. The Company agrees with the ERG's viewpoint that there are no plausible alternative approaches that could be used to fit a parametric extrapolation to the RWE OS data.

It is also important to note that, in the Company's revised base case cost-effectiveness analysis, the survival predictions at 5, 10, 15 and 20 years for dostarlimab and current clinical management are underestimated, when compared to the mean clinical expert estimates presented in Table 7 (Issue 7) and Table 11, respectively. Given the inherent uncertainty associated with extrapolation, it is not possible to select curves for either arms which exactly match the clinical expert estimates of long-term survival. However, for the reasons outlined previously, the Company believes that its base case analysis uses the most appropriate OS curves for both dostarlimab and current clinical management.

Finally, the Company is unclear on the ERG's preference to take into consideration the clinical experts' opinions for current clinical management, and yet, to disregard the same opinions for dostarlimab.

Table 11: Proportion of patients predicted to be alive at each timepoint following treatment with current clinical management compared with mean clinical expert estimates

Time	Modelled OS for current clinical management (RWEQ, log-logistic)	Mean clinical expert estimates for OS for patients treated with current clinical management

		3 years [redacted] [redacted] 5 years [redacted] [redacted] 10 years [redacted] [redacted] 15 years [redacted] [redacted] 20 years [redacted] [redacted] **Abbreviations:** OS: overall survival; RWEQ: real-world equivalent; NA: not applicable.
Key issue 9: Dostarlimab time to treatment discontinuation (TTD) elicitation exercise and treatment discontinuations	Yes	**The Company maintains that the [redacted] cessation percentage, as well as the starting point and duration of treatment waning included in its base case cost-effectiveness analysis for dostarlimab, represent the most appropriate assumptions. The Company has proposed a revised version of the ERG's treatment waning methodology that accounts for patients who discontinue treatment with dostarlimab after [redacted] (noting that [redacted]% of patients are modelled to receive dostarlimab for a total of [redacted].** **TTD expert elicitation and the derivation of the percentage of patients remaining on treatment with dostarlimab beyond [redacted]** The Company notes that the clinical experts were presented with data for the number of patients at risk of discontinuing treatment with dostarlimab, *in lieu* of the appropriate ToT KM data from GARNET, which was unfortunately not available for the expert elicitation process. The Company believes that the ERG has misinterpreted the 'cliff-edge' observed in the Company's dostarlimab ToT curve, once adjusted for anticipated real-world prescribing. The 'cliff-edge' observed in the current base case cost-effectiveness analysis is heavily influenced by the overestimated ToT KM curve at [redacted] with only [redacted] patients (<[redacted]) at risk of treatment discontinuation beyond 21 months. Censoring towards the end of the tail (i.e. patients who had a shorter follow-up of less than [redacted] were censored even though they may have still been receiving treatment with dostarlimab), together with the remaining patients exhibiting durable responses in GARNET, led to the plateau observed in the ToT KM data from Month 21 onwards and may reflect an overestimation of the probability of patients remaining on treatment at [redacted] and beyond. It is therefore likely that the 'cliff-edge' between the "true" ToT in GARNET at [redacted],

		and the [redacted]% that is currently modelled, would be substantially reduced when longer-term follow-up data are available from GARNET. It should also be noted that the ToT adjustment to assume that [redacted]% of patients remain on treatment after [redacted] is consistent with the Company's approach to the clinical expert estimates for PFS and OS. The Company has aligned modelled ToT with the lower end of these clinical estimates. In this case, there is uncertainty about the probability of remaining on treatment with dostarlimab for longer than [redacted], and whether it would be any higher than [redacted]%. Therefore, the Company believes that the use of [redacted]% represents the most appropriate assumption. **The Company's revised version of the ERG's treatment waning methodology** As mentioned previously in the Company response to Key Issue 6, the original Company and the ERG's treatment waning approaches were both oversimplified, because they assumed that all patients discontinue treatment with dostarlimab at [redacted]. However, according to the Company's current base case assumptions, [redacted]% of patients continue to receive treatment with dostarlimab beyond [redacted], and of these, [redacted] continue to receive treatment until the end of [redacted] ([redacted]% of the total population of patients who receive treatment with dostarlimab). It is therefore extremely conservative to apply treatment waning to all patients in the dostarlimab arm from the end of [redacted]. Using the ERG's methodology, a patient who discontinues dostarlimab after five years of treatment is assumed, at [redacted] to immediately transition to a hazard of death equal to the hazard of death at the same timepoint for a patient who initially started treatment with current clinical management. The ERG's approach therefore assumes that patients who continue to receive dostarlimab after [redacted] incur the full costs of their treatment, but they do not experience any additional benefit. In order to mitigate these limitations, the Company has proposed a revised version of the ERG's treatment waning approach, which accounts for the fact that some patients remain on treatment with dostarlimab for longer than [redacted]. The delay to treatment waning following discontinuation of treatment with dostarlimab ([redacted]) and the duration of waning ([redacted] after waning begins) are

		unchanged from the Company's base case cost-effectiveness analysis, however, treatment waning is no longer applied to all patients at the same time. A detailed summary of this approach is provided in Appendix 4. The implementation of this into the model changes the Company's revised base case ICER from £49,608 to £48,608, a reduction of £1,000. **The Company's treatment waning assumptions** The Company would like to reiterate that the starting point and the duration of treatment waning in the Company's revised treatment waning approach have remained unchanged from the Company's base case cost-effectiveness analysis. These assumptions were based on clinical expert opinion, as well as a considerable, and growing, body of published evidence that represents the best available proxy, highlighting the potential for long-term survival and continued treatment benefit associated with I-O therapies with the same mechanism of action as dostarlimab. Initially, it is important to note the responses of two clinicians who were asked to estimate how long the treatment effect of dostarlimab would continue, and when treatment waning would take effect.[17] The slide that was presented to both clinical experts is presented in the reference pack alongside this response. Of note, the clinical experts were asked: • Would you expect a continued treatment benefit with dostarlimab after discontinuation; for OS? For PFS? • Would you expect there to be a drop off in this efficacy after a certain period? • If you do believe a waning effect is plausible, what time point would a treatment waning effect begin? o At the start of treatment o At treatment discontinuation o 3 months post-treatment discontinuation o 6 months post-discontinuation

		o 12 months post discontinuation o >12 months post discontinuation • After this time point, how long would it take for treatment effect to wane completely o 1 year o 1.5 years o 2 years o 2.5 years o 3 years o >3 years The anonymised minutes summarising these discussions were provided in response to ERG Clarification Question C3 and are provided as references alongside this response document as well. The relevant discussions are summarised on Pages 4–6 of the file entitled "GSK Data on File. 1-1 Meetings. Time-on-Treatment".[17] Notably, both clinical experts indicated that any waning of treatment effect for dostarlimab would not begin immediately post-treatment discontinuation, with the two clinicians noting that it would likely start between [redacted], and [redacted], respectively. Thus, clinical expert feedback provides no justification to support the ERG's preferred assumption, where treatment waning begins immediately after treatment discontinuation. When determining the most appropriate treatment waning assumptions, the Company also considered the body of published evidence of other I-O appraisals, to incorporate the best available proxy data into the decision-making process. This includes, but is not limited to, a considerable number of NICE appraisals for nivolumab and pembrolizumab, two I-O therapies with the same mechanism of action as dostarlimab. Across multiple appraisals for nivolumab and pembrolizumab, NICE have accepted that a treatment effect duration of between three to five years is plausible when patients discontinue treatment with an I-O therapy after two years. In this regard, the Company's treatment waning approach could be considered conservative, given that patients are

		only assumed to experience a [redacted] after discontinuing treatment, and the treatment effect is linearly reducing for [redacted] out of these [redacted] years. The conservative nature of the Company's base case cost-effectiveness analysis is supported by some of the Committee's preferred assumptions in previous I-O appraisals, where the treatment effect was not assumed to decline between stopping treatment and the duration at which treatment benefit was ceased. For example, TA490 and TA661 both considered long-term treatment duration assumptions whereby a full treatment effect was assumed to exist for three years after stopping treatment with the I-O therapy, after which point, a HR of 1 was applied to model OS for the intervention versus the comparator.[18, 19] Similarly, TA724 simply assumed that the mortality rate of the intervention was set to equal to that of the comparator from the treatment effect cessation timepoint onwards, rather than a gradual treatment waning effect as applied in this appraisal.[20] Accordingly, the Company believes that the treatment waning assumptions applied in its base case cost-effectiveness analysis, where treatment waning begins [redacted] after the discontinuation of treatment, and linearly declines over the following [redacted] before the hazard of death for dostarlimab is set equal to the hazard of death for the comparator, is a reasonable and justified approach. In order to explore a plausible range of uncertainty, the Company has undertaken a scenario where treatment waning begins [redacted] months after the discontinuation of treatment with dostarlimab, lasting for [redacted] years. The resulting ICER for this Scenario 7 (Table 16), of £49,831, is very similar to the base case ICER of £48,608, demonstrating that the exact starting points and duration of treatment waning do not represent a major source of uncertainty.
Key issue 10: Dostarlimab choice of TTD curve	Yes	**The Company have incorporated the updated GARNET ITT ToT for dostarlimab, as provided in response to Clarification Question A6, as part of its revised base case cost-effectiveness analysis. The lognormal extrapolation now represents the most appropriate curve choice for dostarlimab ToT.** The Company acknowledge that there was a minor difference between the GARNET ITT ToT data

provided as part of the original submission compared with the data provided in response to Clarification Question A6, due to slightly alternative methods of analysing the KM data. The Company can confirm that the data provided in response to Clarification Question A6 represent the more accurate data for the ITT ToT population, and this has therefore been updated in the Company's revised base case cost-effectiveness analysis.

The standard parametric distributions considered in the CS were fitted to the updated ToT data for the GARNET ITT population. The AIC and BIC values for each of the extrapolations are summarised in Table 12, and extrapolations of ToT using each parametric function up to five years are presented in Figure 8.

Table 12: Summary of goodness-of-fit data for dostarlimab ToT (GARNET ITT population) standard parametric models

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; ToT: time on treatment.

Figure 8: Dostarlimab ToT extrapolations up to five years, prior to adjustment for anticipated real-world prescribing (GARNET ITT population)

		 **Abbreviations**: ITT: intention-to-treat; ToT: time on treatment. The Generalised gamma extrapolation provides the best statistical fit to the updated GARNET ITT ToT data, followed by the lognormal extrapolation. However, the plateaus associated with the Generalised gamma, as well as the Gompertz extrapolation and the splines, were considered to be clinically implausible, modelling an extremely low rate of treatment discontinuation with dostarlimab after two years, which is unlikely to be the best representation of real-world prescribing of dostarlimab in the UK clinical setting. As such, the Company preference is to use the second best statistically fitting extrapolation, lognormal, in its revised base case cost-effectiveness analysis. **Figure 9: Dostarlimab ToT extrapolations up to five years, following adjustment for anticipated real-world prescribing at two years (GARNET ITT population)**

		 **Abbreviations**: ITT: intention-to-treat; ToT: time on treatment. In line with the approach taken in the original CS, and detailed in Key Issue 9, an adjustment to the ToT curve was applied to reflect the anticipated real-world prescribing of dostarlimab, assuming that [redacted]% of patients continue to receive treatment with dostarlimab after [redacted], and after [redacted], all remaining patients are assumed to discontinue treatment. The incorporation of the updated GARNET ITT ToT data, and the selection of the lognormal curve versus the log-logistic in the Company's previous base case was associated with a minor impact to the base case ICER. The incremental increase to the Company's original base case ICER was [redacted].
Key issue 11: Censoring and the	No	**The Company does not believe that a comparison between censoring in GARNET and censoring in the RWEQ is appropriate for the reasons outlined below, and therefore this**

possibility of informative censoring		**issue should not be considered a major source of uncertainty.** Initially, it is important to note that the Company are unable to provide the requested data, including GARNET KM data restricted to patients with a CR or PR response because, as previously noted, the reduced sample size associated with these data (N=[redacted]) means that it would not be appropriate to draw any conclusions. Nevertheless, the Company notes that the ERG's concerns relating to this issue are underpinned by Figure 27 in the ERG report, which compares the numbers at risk of death as a proportion of the baseline population of patients in the GARNET and the RWEQ, and notes that there is a higher pattern of censoring in the GARNET study compared to the RWEQ. The Company agrees with the ERG that if a similar pattern of censoring was observed in a randomised controlled trial, this could be a cause for concern, because both groups of patients would be receiving treatment in the same setting (i.e. a clinical trial setting). However, when comparing GARNET with the RWEQ, patients receiving dostarlimab in GARNET and patients receiving current clinical management in the RWEQ are not receiving treatment in the same setting. Patients in GARNET must follow a strict protocol with regard to timings of assessments and the other requirements associated with being in a trial setting. This means that these patients might have more reasons to discontinue treatment with dostarlimab and/or to remove themselves from the trial. In comparison, patients in the RWEQ are not subject to the same strict requirements associated with a trial, and it is not possible for these patients to "remove themselves" from the RWEQ (i.e. real-life current clinical practice) in the same way as it is in GARNET. Consequently, the Company does not believe that a comparison between censoring in GARNET and censoring in the RWEQ is appropriate. There is also a risk of over-interpreting the point estimates in the graph generated with the numbers at risk (Figure 27 in the ERG report). Even though the graph is presented as a percentage, the denominators of the GARNET and RWEQ cohorts are very different (N=129 versus N=[redacted]), and the resulting differences of [redacted]% are difficult to interpret. There is also a cross-over and change in direction between the graphs, which could lead to further misinterpretation of

		these point estimates.
Key issue 12: Reliability of comparing GARNET with the RWEQ	Yes	**The differences noted by the ERG between the scenario analysis versus doxorubicin (in ZoptEC) and versus doxorubicin (in the RWEQ) are substantially influenced by methodological differences between the two scenario analyses. When both scenario analyses are modelled via independently fitting extrapolations to both arms, the two ICERs versus doxorubicin are both lower than the base case ICER versus RWEQ and suggest the true ICER for dostarlimab versus doxorubicin lies between £35,703 and £46,597.** **The results of the remaining ICERs versus individual treatments from the RWEQ fall within a range of £35,703 (PLD monotherapy, Scenario 13) to £57,954 (carboplatin plus paclitaxel, Scenario 11), suggesting that these values encompass the extremities of uncertainty associated with the base case ICER versus current clinical management. This supports the Company's assertion from Key Issue 5, that the Company's true base ICER versus current clinical management lies between the lower and upper bounds of £43,977 and £55,626.** **Reliability of comparing GARNET with the RWEQ** As noted in Key Issue 4, at this time there is no plan to undertake a randomised controlled trial of dostarlimab in this indication. As outlined in Key Issue 5, whilst it is not possible to adjust for dMMR/MSI-H status between the GARNET and RWEQ populations, substantial effort has been made to adjust for endometrioid disease status, and a MAIC has been conducted between the endometrioid cohorts of GARNET and the RWEQ. Together these analyses may help to indicate the upper bound of the Company's base case ICER versus current clinical management. **Methodological differences between scenario analyses resulting in discrepancies** The ERG noted differences between the ICER versus doxorubicin (where doxorubicin PFS and OS are derived from independent extrapolations of the RWEQ data for doxorubicin alone) compared to the ICER versus doxorubicin (where doxorubicin OS was derived by applying the matching-adjusted HR from the IPTW ITC between GARNET and ZoptEC to the dostarlimab OS curve, and

		doxorubicin PFS was derived by applying the matching-adjusted HR from the MAIC versus the published Makker et al. [2013] study).[21] The ERG's interpretation of this discrepancy was that the comparison between GARNET and the RWEQ is biased in favour of dostarlimab. However, the Company notes that there are important methodological differences between these two scenario analyses which may cause these discrepancies, rather than differences between the patient populations. In particular, as detailed in Additional Issue 1, modelling comparator efficacy by applying a HR to the corresponding dostarlimab OS/PFS curves is associated with substantial uncertainty, and the Company believes that independently fitting extrapolations to PFS and OS for both dostarlimab and the comparators represents the most robust approach, where possible. **Scenario analysis between dostarlimab (GARNET) and doxorubicin (ZoptEC)** In order to characterise the extent to which this methodology causes discrepancies between the ICERs versus doxorubicin (ZoptEC) and doxorubicin (RWEQ), the Company has explored fitting independent extrapolations to matching-adjusted KM data for both dostarlimab and doxorubicin (derived from the IPTW ITC between GARNET and ZoptEC). Matching-adjusted OS KM data following IPTW was previously discussed in the CS, Document B, Section B.2.7.2.1. Since the CS, the Company has also conducted a matching-adjusted analysis between PFS for dostarlimab (GARNET) and doxorubicin (ZoptEC), using modified assessment-schedule matching. Full details of this analysis are outlined in Appendix 2. This allowed independent extrapolations to be fitted to the matching-adjusted PFS KM data in addition. Full details of the statistical fit, as well as extrapolations over 5 years and 40 years for all of the parametric curves for dostarlimab and doxorubicin PFS and OS are presented in Appendix 2. The chosen extrapolations for this scenario analysis are outlined in Table 29, Appendix 2. The Company believes that the use of independent extrapolations for PFS and OS for both dostarlimab and doxorubicin is the most appropriate approach for any scenario analysis versus the

		doxorubicin in the ZoptEC trial, given the substantial limitations assuming the PH assumption between dostarlimab and chemotherapy. This means that the application of HRs to the dostarlimab curves is not appropriate, as highlighted in Additional Issue 1. It is also necessary to determine whether dostarlimab OS and PFS should be waned to the RWEQ curves or to the individual doxorubicin curves. The Company acknowledges that there is some uncertainty here, and therefore has presented scenario analyses using both approaches in Table 15 below. **Scenario analyses versus individual treatments based on the RWEQ** **In addition to the matching-adjusted scenarios presented versus doxorubicin in ZoptEC, the Company has conducted scenarios versus the individual treatments based on the naïve individual treatment data from the RWEQ. The results of these ICERs fall within a range of £35,703 (PLD monotherapy, Scenario 13) to £57,954 (carboplatin plus paclitaxel, Scenario 11), suggesting that these values encompass the extremities of uncertainty associated with the base case ICER versus current clinical management.** The Company has conducted these scenario analyses in order to allow comparison of the scenario analyses versus doxorubicin as well as, for completeness, to explore the range of uncertainty associated with the base case cost-effectiveness analysis. Nevertheless, given the lack of standard of care treatments available for patients in this setting, and as highlighted throughout the CS, the Company believes that the base case comparison versus current clinical management provides the most appropriate source of evidence, including the whole range of treatments currently used in UK clinical practice, rather than focussing on any one comparator. The Company has used the log-logistic extrapolation for PFS and OS for each of the individual treatments, in order to ensure that any differences between these scenario analyses result from the differences in the costs and outcomes associated with the individual treatments only, rather than the different shapes and hazard profiles associated with the chosen curves in each scenario

analysis. The log-logistic curve is also the best fitting curve in the majority of cases.

The importance of this is outlined in Table 13, which presents the incremental LYs gained for dostarlimab versus each of the individual comparators, when the statistically best fitting extrapolations are used for the comparator PFS and OS in all cases.

Table 13: Statistically best-fitting OS and PFS extrapolations for individual treatment scenario analyses based on the RWEQ

Comparator	Comparator OS statistically best-fitting extrapolation	Comparator PFS statistically best-fitting extrapolation	Incremental LYs gained for dostarlimab versus comparator (Waning dostarlimab to overall RWEQ curve)	Incremental LYs gained for dostarlimab versus comparator (Waning dostarlimab to individual treatment RWEQ curve)
Carboplatin plus paclitaxel	Log-logistic	Log-logistic	[redacted]	[redacted]
Carboplatin monotherapy	Lognormal	Weibull	[redacted]	[redacted]
PLD monotherapy	Log-logistic	Log-logistic	[redacted]	[redacted]
Paclitaxel monotherapy	Exponential	Gamma	[redacted]	[redacted]
Carboplatin plus PLD	Log-logistic	Log-logistic	[redacted]	[redacted]

Abbreviations: LYs: life years; OS: overall survival; PLD: pegylated liposomal doxorubicin; PFS: progression-free survival; RWEQ: real-world equivalent.

In some cases, the selection of different curves for OS and PFS for each of the individual

		treatments results in clinically implausible results. When dostarlimab is waned to the RWEQ curve, it is associated with [redacted] and [redacted] LYs gained versus the two platinum-doublet chemotherapy regimens, and between [redacted] to [redacted] LYs gained versus the three monotherapy chemotherapy regimens, in line with the relative efficacy of each treatment. However, when dostarlimab is waned to the individual treatment RWEQ curves, the results suggest the treatment effect of dostarlimab is the lowest when compared to paclitaxel monotherapy, out of the five treatments included in the RWEQ basket. Dostarlimab gains only [redacted] LYs versus paclitaxel monotherapy, compare to a gain of [redacted] LYs versus carboplatin plus paclitaxel, and a gain of [redacted] LYs versus PLD monotherapy. Based on the relative efficacies associated with each treatment, it is not clinically plausible for dostarlimab to result in a reduced treatment effect versus paclitaxel monotherapy compared with carboplatin plus paclitaxel, nor for the treatment effect versus paclitaxel monotherapy and versus PLD monotherapy to be widely different. Similarly, dostarlimab gains almost the same number of LYs versus carboplatin monotherapy ([redacted]) and versus carboplatin plus PLD ([redacted]) when dostarlimab is waned to the individual comparator curve, suggesting the treatment effect of dostarlimab is the same versus both comparators. This is not clinically plausible, given the improved efficacy associated with carboplatin plus PLD versus carboplatin monotherapy. In comparison, a summary of the LYs gained using the Company's preferred log-logistic extrapolations for PFS and OS for each of the individual comparators is presented in Table 32 in Appendix 5. To ensure each of the scenario analyses remained clinically plausible, the Company used the log-logistic extrapolation to model both PFS and OS for each comparator in each of the individual treatment scenario analyses presented below. Given the minimal impact on clinical plausibility in terms of the TTD curve choice, the best

statistically fitting TTD curve was used for each comparator. The same curve is used for all of the monotherapy chemotherapies (Weibull) and the platinum doublet chemotherapies (log-logistic), which the Company believes is appropriate.

A summary of the chosen PFS, OS and TTD extrapolations for each of the individual comparators is presented in Table 14.

Table 14: Company preferred PFS, OS and TTD extrapolations for scenario analyses versus the individual treatments from the RWEQ

Comparator	Chosen comparator PFS extrapolation	Chosen comparator OS extrapolation	Chosen comparator TTD extrapolation
Carboplatin plus paclitaxel	Log-logistic	Log-logistic	Log-logistic
Carboplatin monotherapy	Log-logistic	Log-logistic	Weibull
PLD monotherapy	Log-logistic	Log-logistic	Weibull
Paclitaxel monotherapy	Log-logistic	Log-logistic	Weibull
Carboplatin plus PLD	Log-logistic	Log-logistic	Log-logistic

Abbreviations: OS: overall survival; PLD: pegylated liposomal doxorubicin; PFS: progression-free survival; RWEQ: real-world equivalent: TTD; time to discontinuation.

Results of scenario analyses versus individual treatments

Table 15: Additional scenario analyses versus individual treatments

Scenario Number	Comparator	Treatment waning to overall RWEQ PFS and OS curves	Treatment waning to individual treatment PFS and OS curves

				ICER (£/QALY)	ICER (£/QALY)
		Scenario analyses versus doxorubicin monotherapy based on the IPTW ITC between dostarlimab (GARNET) and doxorubicin (ZoptEC)			
		9	**Doxorubicin monotherapy[a]** • Dostarlimab PFS and OS: As per base case • Doxorubicin PFS: Matching-adjusted PFS HR ([redacted]) (derived from the ITC between GARNET and ZoptEC) applied to independently extrapolated unmatched GARNET KM data • Doxorubicin OS: Matching-adjusted OS HR ([redacted]) (derived from the ITC between GARNET and ZoptEC) applied to independently extrapolated unmatched GARNET KM data	£62,971	£42,611
		10	**Doxorubicin monotherapy[a]** • Dostarlimab PFS: Independent extrapolation (lognormal) of matching-adjusted GARNET KM data (derived from the ITC between GARNET and ZoptEC) • Doxorubicin PFS: Independent extrapolation (log-logistic) of matching-adjusted ZoptEC KM data (derived from the ITC between GARNET and ZoptEC) • Dostarlimab OS: Independent extrapolation (Generalised gamma) of matching-adjusted GARNET KM data (derived from the ITC between GARNET and ZoptEC) • Doxorubicin OS: Independent extrapolation (log-logistic) of matching-adjusted ZoptEC KM data (derived from the ITC between GARNET and ZoptEC)	£45,634	£46,597
			Scenario analyses versus individual comparators, based on individual comparator data from the RWEQ		
		11	**Carboplatin plus paclitaxel** • Dostarlimab PFS and OS: As per base case	£56,060	£57,954

				• Carboplatin plus paclitaxel PFS, OS and TTD: Independent extrapolation of unmatched individual treatment RWEQ data (PFS: loglogistic, OS: loglogistic, TTD: loglogistic)		
			12	**Carboplatin monotherapy** • Dostarlimab PFS and OS: As per base case • Carboplatin monotherapy PFS, OS and TTD: Independent extrapolation of unmatched individual treatment RWEQ data (PFS: loglogistic, OS: loglogistic, TTD: Weibull)	£43,528	£49,123
			13	**PLD monotherapy[a]** • Dostarlimab PFS and OS: As per base case • PLD monotherapy PFS, OS and TTD: Independent extrapolation of unmatched individual treatment RWEQ data (PFS: loglogistic, OS: loglogistic, TTD: Weibull)	£35,703	£38,698
			14	**Paclitaxel monotherapy** • Dostarlimab PFS and OS: As per base case • Paclitaxel monotherapy PFS, OS and TTD: Independent extrapolation of unmatched individual treatment RWEQ data (PFS: loglogistic, OS: loglogistic, TTD: Weibull)	£41,490	£40,715
			15	**Carboplatin plus PLD** • Dostarlimab PFS and OS: As per base case • Carboplatin plus PLD PFS, OS and TTD: Independent extrapolation of unmatched individual treatment RWEQ data (PFS: loglogistic, OS: loglogistic, TTD: loglogistic)	£48,854	£53,714

[a] The cost of doxorubicin monotherapy is modelled as a weighted average of [redacted]% of patients receiving "naked" doxorubicin monotherapy and [redacted]% of patients receiving PLD monotherapy, based on the proportions of patients receiving each treatment in the UK RWE study.
Abbreviations: HR: hazard ratio; ITC: indirect treatment comparison; KM: Kaplan-Meier; LYG: life-years gained; OS: overall survival; PLD: pegylated liposomal doxorubicin; PFS: progression-free survival; RWEQ: real-world equivalent; TTD: time to discontinuation.

		It is important to note that all of the ICERs versus doxorubicin/PLD monotherapy, when doxorubicin OS is derived via independently fitted extrapolations (Scenario 10 and Scenario 13), are lower than the Company's base case cost-effectiveness analysis. These ICERs suggest that the true ICER versus doxorubicin likely lies between a lower range of £35,703, and an upper range of £46,597. The large discrepancy between the ICER versus doxorubicin (ZoptEC, when doxorubicin OS is derived via a HR, Scenario 9) of £62,971, and the ICER versus doxorubicin (ZoptEC, when doxorubicin OS is derived via independent extrapolation, Scenario 10) of £45,634 underlines the limitations associated with the HR-based methodology as discussed below in Additional issue 1. These results therefore indicate that the ERG's concerns regarding the discrepancy between the doxorubicin comparisons based on ZoptEC and the RWEQ in Key issue 12 are largely influenced by the previously discussed differences in methodologies between the two scenario analyses, rather than differences in the patient populations between the two studies. The results of the remaining ICERs fall within a range of £35,703 (PLD monotherapy, Scenario 13) to £57,954 (carboplatin plus paclitaxel, Scenario 11), suggesting that these values encompass the extreme lower and upper bounds of uncertainty associated with the base case ICER versus current clinical management. Across most individual treatment scenarios, there is minimal difference between the two waning choices (waning to the overall RWEQ curves, or the individual treatment curves), when PFS and OS for the comparator are derived via independent extrapolation. However, a larger discrepancy between the two approaches is observed when the comparator efficacy is derived via a HR, such as Scenario 9 (Table 15), where dostarlimab and doxorubicin are compared using a HR from the ZoptEC IPTW ITC to derive the efficacy of doxorubicin from dostarlimab. When considering the substantial limitations associated with HRs detailed in Additional Issue 1, and the likely violation of the PH assumption, Scenario 9 should be interpreted with extreme caution, and does not provide relevant evidence to inform the decision about whether to wane to the RWEQ or the individual comparator.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Use of independent extrapolations versus hazard ratios to model PFS and OS	NA	No	**The use of hazard ratios to derive comparator efficacy estimates versus dostarlimab is inappropriate, given the fundamental differences in mechanism of action between dostarlimab and chemotherapies, and likely violations of the PH assumption. Deriving comparative efficacy estimates by independently fitting extrapolations to both arms represents a more appropriate approach.** As discussed in the CS Document B, Section B.3.3.6, the fitting of independent parametric models, rather than the application of HRs, was considered to be a more appropriate approach in the base case cost-effectiveness analysis. This is due to the fundamental difference in mechanism of action between dostarlimab and the cytotoxic chemotherapies that constitute current clinical management. As outlined previously in response to Key Issue 7, there is a clear pattern observed with I-O therapies whereby there is a delay in benefit as the immune system is activated, whilst chemotherapy acts immediately on the cancer cells.[2] This pattern is therefore not reflective of a situation where PH might apply.

			The application of a HR to the dostarlimab PFS and OS extrapolations inherently assumes that the comparator chemotherapy will be associated with survival functions that display a similar shape and follow a similar trajectory to the dostarlimab survival functions, including the potential for long-term benefit and the extended tail of the KM curves that is the hallmark of I-O therapies. Based on the published evidence of chemotherapy for patients with recurrent or advanced EC in the post-platinum setting, this assumption was considered unlikely. It should be noted that whilst clear violation of the PH assumption was observed for PFS between dostarlimab and current clinical management, it was not possible to conclusively determine whether the PH assumption was violated for OS. However, based on the clinical rationale discussed above, the Company believes that longer-term follow-up data from the GARNET trial would likely demonstrate that the PH assumption would also be violated between OS for dostarlimab versus current clinical management (as well as dostarlimab versus doxorubicin in the ZoptEC trial). Finally, it is important to note that any scenario which models comparator efficacy using a HR applied to the dostarlimab curve, and then applies treatment waning to the dostarlimab curve, inherently violates the PH assumption. Thus, the Company believes that all scenario analyses based on HRs must be interpreted with extreme caution, given the substantial limitations associated with the use of HRs in this appraisal, where the PH assumption is unlikely to apply. The Company believes that the fitting of independent parametric models to model efficacy for both dostarlimab and the comparator of interest, represents a more robust approach.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

The revised Company base case ICER being submitted as part of this response is provided below, alongside details of the changes made from the CS base case ICER. The impact of each change made in isolation on the original Company base case ICER [redacted] is presented in the final column.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the Company's base-case ICER
NA	[redacted]	[redacted]	[redacted]
Key Issue 6	The Company used hazard ratios to apply treatment waning. The treatment waning methodology in the base case cost-effectiveness analysis assumed that all patients discontinued treatment at the first cessation point, and therefore applied treatment waning to all patients, even those who remained on treatment.	The Company has incorporated an adapted version of the ERG's revised treatment waning methodology, whereby treatment waning is only applied to patients once they discontinue treatment.	[redacted]
Key Issue 6	The ERG identified that there was an error in the calculation of the percentage of	The Company have incorporated the ERG's correction to the calculation of the [redacted]	[redacted]

	patients who continue to receive dostarlimab beyond the first cessation point.	cessation percentage into the revised base case cost-effectiveness analysis.	
Key Issue 6	Patients were assumed to receive 0.5 doses of dostarlimab once every three weeks from the 5th administration onwards.	The Company have incorporated the ERG's revised methodology (once it was corrected), which assumes that patients receive 1 dose of dostarlimab every six weeks from the 5th administration onwards.	[redacted]
Key Issue 6	The resource use assumptions detailed in the CS, Document B, Section B.3.5, were used in the cost-effectiveness analysis.	The ERG's preferred resource use assumptions have been incorporated into the base case cost-effectiveness analysis.	[redacted]
Key Issue 10	TOT for the ITT population had been implemented incorrectly in the cost-effectiveness analysis. A log-logistic curve was previously selected to model TOT prior to adjustment for anticipated real-world prescribing.	The Company has updated the ITT TTD data for the N=129 population. The lognormal curve is now selected to model TOT prior to adjustment for anticipated real-world prescribing. This adjustment is still applied, meaning that [redacted]% of patients continue to receive treatment with dostarlimab following [redacted].	[redacted]
Company's preferred base case following technical engagement	**Incremental costs: £**[redacted]	**Incremental QALYs:** [redacted]	**ICER: £48,608**

Abbreviations: CS: Company submission; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; PAS: patient access scheme; QALY: quality-adjusted life year; ToT: time on treatment; TTD: time to treatment discontinuation.

Revised Company base case and scenario analyses

Following technical engagement, the company's revised base case ICER is £48,608. The Company notes that this ICER may be conservative, as it represents a naïve comparison between dostarlimab (GARNET) and current clinical management (RWEQ). The Company's MAICs versus the RWEQ indicate that the naïve comparison may underestimate the true treatment effect associated with dostarlimab; when an independent extrapolation is fitted to the matching-adjusted GARNET OS KM data from the MAIC Scenario 1, the resulting ICER is £43,977. The Company therefore believes that the true base case ICER for the population under consideration might lie somewhere between £43,977 and £48,608. A range of other scenario analyses are also presented in Table 16 (versus current clinical management) and Table 17 (exploratory scenario analyses versus individual treatments) below.

Table 16: Revised Company base case and associated scenario analyses

No.	Description	[redacted] for dostarlimab		
		Incr. costs	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	£48,608
Scenario analyses based on the MAIC between GARNET and RWEQ				
1	RWEQ OS: Matching-adjusted HR ([redacted]) applied to independently extrapolated unmatched GARNET KM data – MAIC Scenario 1	[redacted]	[redacted]	£41,541
2	Dostarlimab OS: Independent extrapolation of matching-adjusted GARNET KM data (Generalised gamma) – MAIC Scenario 1	[redacted]	[redacted]	£43,977
Scenario analyses based on endometrioid cohorts of GARNET and the RWEQ				
3	• Dostarlimab PFS: Independent extrapolation of unmatched endometrioid GARNET KM data (Log-logistic) • RWEQ PFS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic) • Dostarlimab OS: Independent extrapolation of unmatched endometrioid GARNET KM data (Generalised gamma) • RWEQ OS: Matching-adjusted HR ([redacted]) applied to independently extrapolated unmatched endometrioid GARNET KM data – MAIC Scenario 1	[redacted]	[redacted]	£48,614
4	• Dostarlimab PFS: Independent extrapolation of unmatched endometrioid GARNET KM data (Log-logistic)	[redacted]	[redacted]	£53,437

	• RWEQ PFS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic) • Dostarlimab OS: Independent extrapolation of matching-adjusted endometrioid GARNET KM data (Generalised gamma) – MAIC Scenario 1 • RWEQ OS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic)			
5	• Dostarlimab PFS: Independent extrapolation of unmatched endometrioid GARNET KM data (Log-logistic) • RWEQ PFS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic) • Dostarlimab OS: Independent extrapolation of unmatched endometrioid GARNET KM data (Generalised gamma) • RWEQ OS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic)	[redacted]	[redacted]	£55,626
Other scenario analyses				
6	Dostarlimab ITT ToT curve: Generalised gamma (compared to lognormal in the base case)	[redacted]	[redacted]	£50,111
7	Treatment waning begins [redacted] after treatment discontinuation, and is applied for [redacted] (compared to waning beginning [redacted] after treatment discontinuation and applied for [redacted] in the base case)	[redacted]	[redacted]	£49,831
8	Treatment waning is applied using the ERG's approach alone (prior to the Company's revisions to account for the timepoints at which patients discontinue treatment)	[redacted]	[redacted]	£49,608

Abbreviations: ERG: Evidence Review Group; HR: hazard ratio; incr.: incremental; ICER: Incremental cost-effectiveness ratio; ITT: intention-to-treat; KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; RWEQ: real-world evidence equivalent; ToT: time on treatment.

Table 17: Additional scenario analyses versus individual comparators, based on comparator efficacy using independent extrapolations to individual treatment data from the RWEQ

No.	Comparator	Treatment waning to overall RWEQ PFS and OS curves			Treatment waning to individual comparator PFS and OS curves		
		Incr. costs	Incr. QALYs	ICER (£/QALY)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Scenario analyses based on the IPTW ITC between dostarlimab (GARNET) and doxorubicin (ZoptEC)							
9	**Doxorubicin monotherapy[a]** • Dostarlimab PFS and OS: As per base case • Doxorubicin PFS: Matching-adjusted PFS HR ([redacted]) (derived from the ITC between GARNET and ZoptEC) applied to independently extrapolated unmatched GARNET KM data • Doxorubicin OS: Matching-adjusted OS HR ([redacted]) (derived from the ITC between GARNET and ZoptEC) applied to independently extrapolated unmatched GARNET KM data	[redacted]	[redacted]	£62,971	[redacted]	[redacted]	£42,611
10	**Doxorubicin monotherapy[a]** • Dostarlimab PFS: Independent extrapolation (lognormal) of matching-adjusted GARNET KM data (derived from the ITC between GARNET and ZoptEC) • Doxorubicin PFS: Independent extrapolation (log-logistic) of matching-adjusted ZoptEC KM data (derived from the ITC between GARNET and ZoptEC) • Dostarlimab OS: Independent extrapolation (Generalised gamma) of matching-adjusted GARNET KM data (derived from the ITC between GARNET and ZoptEC) • Doxorubicin OS: Independent extrapolation (log-logistic) of matching-adjusted ZoptEC KM data (derived from the ITC between GARNET and ZoptEC)	[redacted]	[redacted]	£45,634	[redacted]	[redacted]	£46,597
Scenarios versus individual comparators based on individual comparator data from the RWEQ							
11	**Carboplatin plus paclitaxel**	[redacted]	[redacted]	£56,060	[redacted]	[redacted]	£57,954

	• Dostarlimab PFS and OS: As per base case • Carboplatin plus paclitaxel PFS, OS and TTD: Independent extrapolation of unmatched individual treatment RWEQ data (PFS: loglogistic, OS: loglogistic, TTD: loglogistic)						
12	**Carboplatin monotherapy** • Dostarlimab PFS and OS: As per base case • Carboplatin monotherapy PFS, OS and TTD: Independent extrapolation of unmatched individual treatment RWEQ data (PFS: loglogistic, OS: loglogistic, TTD: Weibull)	[redacted]	[redacted]	£43,528	[redacted]	[redacted]	£49,123
13	**PLD monotherapy[a]** • Dostarlimab PFS and OS: As per base case • PLD monotherapy PFS, OS and TTD: Independent extrapolation of unmatched individual treatment RWEQ data (PFS: loglogistic, OS: loglogistic, TTD: Weibull)	[redacted]	[redacted]	£35,703	[redacted]	[redacted]	£38,698
14	**Paclitaxel monotherapy** • Dostarlimab PFS and OS: As per base case • Paclitaxel monotherapy PFS, OS and TTD: Independent extrapolation of unmatched individual treatment RWEQ data (PFS: loglogistic, OS: loglogistic, TTD: Weibull)	[redacted]	[redacted]	£41,490	[redacted]	[redacted]	£40,715
15	**Carboplatin plus PLD** • Dostarlimab PFS and OS: As per base case • Carboplatin plus PLD PFS, OS and TTD: Independent extrapolation of unmatched individual treatment RWEQ data (PFS: loglogistic, OS: loglogistic, TTD: loglogistic)	[redacted]	[redacted]	£48,854	[redacted]	[redacted]	£53,714

[a] The cost of doxorubicin in all doxorubicin monotherapy and PLD monotherapy scenario analyses is modelled as a weighted average of [redacted]% of patients receiving "naked" doxorubicin monotherapy and [redacted]% of patients receiving PLD monotherapy, based on the proportions of patients receiving each treatment in the RWEQ.
Abbreviations: HR: hazard ratio; incr.: incremental; ITC: indirect treatment comparison; ITT: intention-to-treat; OS: overall survival; PLD: pegylated liposomal doxorubicin; PFS: progression-free survival; RWEQ: real-world equivalent.

Appendix 1 Additional data for Key Issue 5

Naive comparison between endometrioid cohorts in GARNET and the RWEQ

Figure 10: PFS KM curves – dostarlimab (naive GARNET endometrioid cohort, N=[redacted]) versus current clinical management (RWEQ endometrioid cohort, N=[redacted])

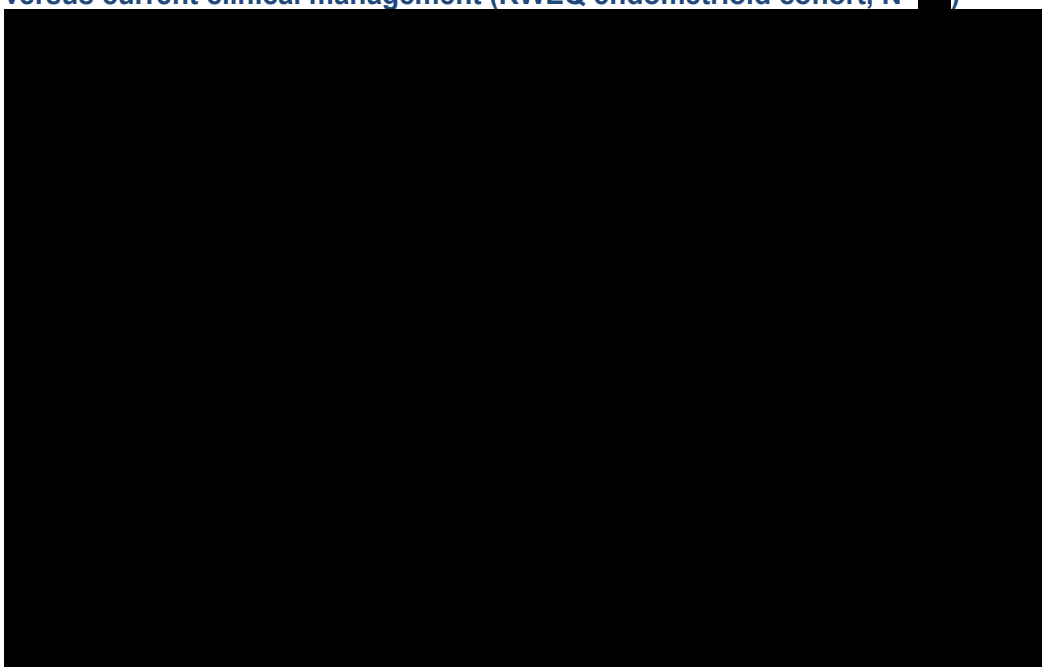
[a] The results presented for the RWEQ use TTNT as a proxy for PFS, as PFS was not recorded in the NCRAS database. [b] Note where the figure states GARNET ITT before matching and RWE cohort base case, **these data reflect the endometrioid cohorts.**
Abbreviations: ITT: intention-to-treat; KM: Kaplan-Meier; PFS: progression-free survival; RWEQ: real-world equivalent.

Figure 11: OS KM curves – dostarlimab (naive GARNET endometrioid cohort, N=[redacted]) versus current clinical management (RWEQ endometrioid cohort, N=[redacted])

[a] Note where the figure states GARNET ITT before matching and RWE cohort base case, **these data reflect the**

endometrioid cohorts.
Abbreviations: ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival; RWE: real-world evidence; RWEQ: real-world equivalent; UK: United Kingdom.

Figure 12: TTD KM curves – dostarlimab (naive GARNET endometrioid cohort, N=[redacted]) versus current clinical management (RWEQ endometrioid cohort, N=[redacted])



[a] Note where the figure states GARNET ITT before matching and RWE cohort base case, **these data reflect the endometrioid cohorts.**
Abbreviations: ITT: intention-to-treat; KM: Kaplan-Meier; RWE: real-world evidence; RWEQ: real-world equivalent; TTD: time to discontinuation; UK: United Kingdom.

Additional data for the MAIC between endometrioid cohorts in GARNET and the RWEQ

Progression-free survival

Table 18: PFS for patients in the GARNET endometrioid cohort (before and after matching) and the RWEQ endometrioid cohort

	Current clinical management (Naïve RWEQ endometrioid cohort) (N=[redacted])[a]	Dostarlimab (Naïve GARNET endometrioid cohort prior to matching) (N=[redacted])	Dostarlimab (Matching-adjusted GARNET endometrioid cohort – MAIC Scenario 1)	Dostarlimab (Matching-adjusted GARNET endometrioid cohort – MAIC Scenario 2)
ESS	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PFS rate at 6 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PFS rate at 12 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PFS rate at 18 months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

[a] The results presented for the RWEQ use TTNT as a proxy for PFS, as PFS was not recorded in the NCRAS database.
Abbreviations: CI: confidence interval; ESS: effective sample size; ITT: intention-to-treat; MAIC: matching-adjusted indirect comparison; NCRAS: National Cancer Registry Analysis System; NE: not estimable; PFS: progression free survival; RWE: real-world evidence; TTNT: time to next treatment.

Figure 13: PFS KM curves – dostarlimab (matching-adjusted GARNET endometrioid cohort, Scenario 1) versus current clinical management (RWEQ endometrioid cohort)

[a] The results presented for the RWEQ use TTNT as a proxy for PFS, as PFS was not recorded in the NCRAS database. [b] Note where the figure states GARNET ITT before matching and RWE cohort base case, **these data reflect the endometrioid cohorts.**
Abbreviations: ITT: intention-to-treat; PFS: progression free survival; KM: Kaplan-Meier; RWE: real-world evidence; RWEQ: real-world equivalent.

Figure 14: PFS KM curves – dostarlimab (matching-adjusted GARNET endometrioid cohort, Scenario 2) versus current clinical management (RWEQ endometrioid cohort)

[a] The results presented for the RWEQ use TTNT as a proxy for PFS, as PFS was not recorded in the NCRAS database. [b] Note where the figure states GARNET ITT before matching and RWE cohort base case, **these data reflect the endometrioid cohorts.**
Abbreviations: ITT: intention-to-treat; PFS: progression free survival; KM: Kaplan-Meier; RWE: real-world evidence; RWEQ: real-world equivalent.

Overall survival

Figure 15: OS KM curves – dostarlimab (matching-adjusted GARNET endometrioid cohort, Scenario 1) versus current clinical management (RWEQ endometrioid cohort)

[a] Note where the figure states GARNET ITT before matching and RWE cohort base case, **these data reflect the endometrioid cohorts.**
Abbreviations: ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival; RWE: real-world evidence; RWEQ: real-world equivalent.

Figure 16: OS KM curves – dostarlimab (matching-adjusted GARNET endometrioid cohort, Scenario 2) versus current clinical management (RWEQ endometrioid cohort)

[a] Note where the figure states GARNET ITT before matching and RWE cohort base case, **these data reflect the endometrioid cohorts.**
Abbreviations: ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival; RWE: real-world evidence; RWEQ: real-world equivalent.

Survival analysis based on naive comparisons of the endometrioid subgroups in GARNET and the RWEQ

Assessment of proportional hazards

Figure 17: Log-cumulative hazard plot between PFS in the naïve GARNET endometrioid cohort and TTNT in the RWEQ endometrioid cohort

Abbreviations: PFS: progression-free survival; RWEQ: real-world equivalent; TTNT: time to next treatment.

Figure 18: Log-cumulative hazard plot between OS in the naïve GARNET endometrioid cohort and OS in the RWEQ endometrioid cohort

Abbreviations: OS: overall survival; RWE: real-world evidence; RWEQ: real-world equivalent; TTNT: time to next treatment.

Progression-free survival

Dostarlimab (endometrioid cohort)

Table 19: Summary of goodness-of-fit data for dostarlimab PFS (naïve GARNET endometrioid cohort) standard parametric models

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Generalised gamma	[redacted]	1	[redacted]	1
Weibull	[redacted]	5	[redacted]	5
Gamma	[redacted]	6	[redacted]	7
Exponential	[redacted]	7	[redacted]	6
Log-logistic	[redacted]	4	[redacted]	4
Lognormal[b]	[redacted]	3	[redacted]	3
Gompertz	[redacted]	2	[redacted]	2

Footnotes: [a] A lower AIC or BIC value represents a better goodness of fit. [b] The Company's preferred extrapolation is the Lognormal.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; PFS: progression-free survival.

Figure 19: Dostarlimab PFS extrapolations (naïve GARNET endometrioid cohort) – up to 5 years - prior to treatment waning

Footnotes: The Company's preferred extrapolation is the Lognormal.
Abbreviations: PFS: progression-free survival.

Figure 20: Dostarlimab PFS extrapolations (naïve GARNET endometrioid cohort) up to 40 years - prior to treatment waning

Footnotes: The Company's preferred extrapolation is the Lognormal.
Abbreviations: PFS: progression-free survival.

Figure 21: Dostarlimab PFS extrapolations (naïve GARNET endometrioid cohort) – up to 5 years –post treatment waning

Footnotes: The Company's preferred extrapolation is the Lognormal.
Abbreviations: PFS: progression-free survival.

Figure 22: Dostarlimab PFS extrapolations (naïve GARNET endometrioid cohort) up to 40 years – post treatment waning

Footnotes: The Company's preferred extrapolation is the Lognormal.
Abbreviations: PFS: progression-free survival.

Current clinical management (endometrioid cohort)

Table 20: Summary of goodness-of-fit data for current clinical management PFS (naïve GARNET endometrioid cohort) standard parametric models

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Generalised gamma	[redacted]	3	[redacted]	3
Weibull	[redacted]	7	[redacted]	7

Gamma	[redacted]	5	[redacted]	5
Exponential	[redacted]	6	[redacted]	6
Log-logistic[b]	[redacted]	1	[redacted]	1
Lognormal	[redacted]	2	[redacted]	2
Gompertz	[redacted]	4	[redacted]	4

Footnotes: [a] A lower AIC or BIC value represents a better goodness of fit. [b] The Company's preferred extrapolation is the log-logistic.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; PFS: progression-free survival.

Figure 23: Current clinical management PFS extrapolations (RWEQ endometrioid cohort) – up to 5 years

Footnotes: The Company's preferred extrapolation is the log-logistic.
Abbreviations: PFS: progression-free survival; RWEQ: real-world equivalent.

Figure 24: Current clinical management PFS extrapolations (RWEQ endometrioid cohort) – up to 40 years

Footnotes: The Company's preferred extrapolation is the log-logistic.
Abbreviations: PFS: progression-free survival; RWEQ: real-world equivalent.

Overall survival

Dostarlimab (endometrioid cohort)

Table 21: Summary of goodness-of-fit data for dostarlimab OS (naïve GARNET endometrioid cohort) standard parametric models

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Generalised gamma[b]	[redacted]	2	[redacted]	5
Weibull	[redacted]	6	[redacted]	6
Gamma	[redacted]	7	[redacted]	7
Exponential	[redacted]	3	[redacted]	1
Log-logistic	[redacted]	4	[redacted]	3
Lognormal	[redacted]	1	[redacted]	2
Gompertz	[redacted]	5	[redacted]	4

Footnotes: [a] A lower AIC or BIC value represents a better goodness of fit. [b] The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; OS: overall survival.

Figure 25: Dostarlimab OS extrapolations (naïve GARNET endometrioid cohort) – up to 5 years – prior to treatment waning

[redacted]

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: OS: overall survival.

Figure 26: Dostarlimab OS extrapolations (naïve GARNET endometrioid cohort) – up to 40 years – prior to treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: OS: overall survival.

Figure 27: Dostarlimab OS extrapolations (naïve GARNET endometrioid cohort) – up to 5 years – post treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: OS: overall survival.

Figure 28: Dostarlimab OS extrapolations (naïve GARNET endometrioid cohort) – up to 40 years – post treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: OS: overall survival.

Current clinical management (endometrioid cohort)

Table 22: Summary of goodness-of-fit data for current clinical management OS (RWEQ endometrioid cohort) standard parametric models

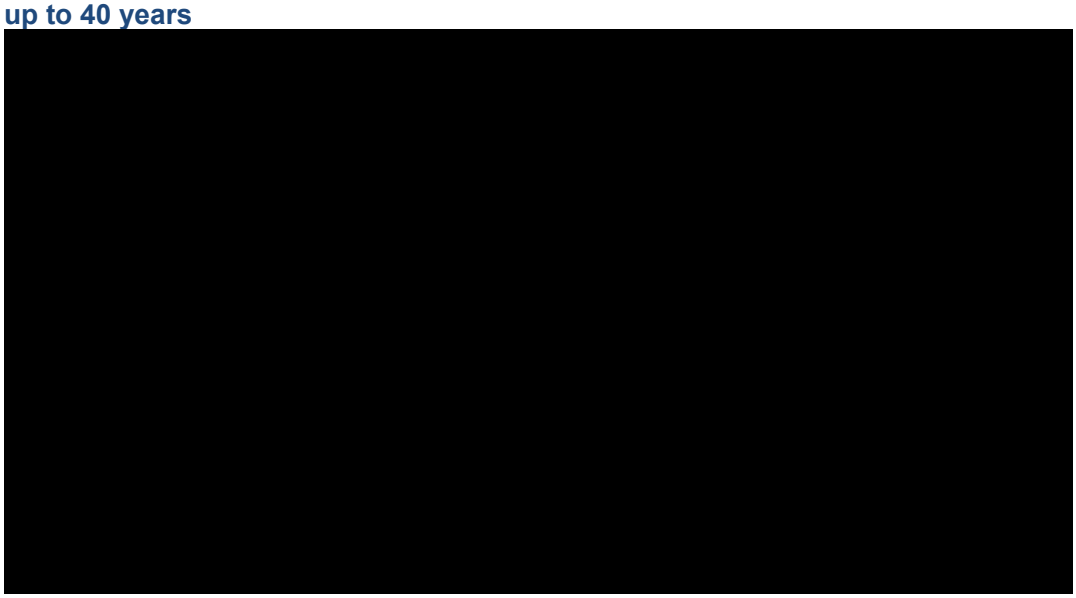
Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Generalised gamma	[redacted]	3	[redacted]	3
Weibull	[redacted]	7	[redacted]	7
Gamma	[redacted]	5	[redacted]	6
Exponential	[redacted]	6	[redacted]	5
Log-logistic[b]	[redacted]	1	[redacted]	1
Lognormal	[redacted]	2	[redacted]	2
Gompertz	[redacted]	4	[redacted]	4

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit. [b] The Company's preferred extrapolation is the log-logistic.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; RWEQ: real-world equivalent; OS: overall survival.

Figure 29: Current clinical management OS extrapolations (RWEQ endometrioid cohort) – up to 5 years

Footnotes: The Company's preferred extrapolation is the log-logistic.
Abbreviations: OS: overall survival; RWEQ: real-world equivalent.

Figure 30: Current clinical management OS extrapolations (RWEQ endometrioid cohort) – up to 40 years



Footnotes: The Company's preferred extrapolation is the log-logistic.
Abbreviations: OS: overall survival; RWEQ: real-world equivalent..

Survival analysis based on matching-adjusted comparisons of the endometrioid cohorts in GARNET and the RWEQ

Overall survival

Dostarlimab (matching-adjusted endometrioid cohort) – MAIC Scenario 1

Table 23: Summary of goodness-of-fit data for dostarlimab OS (matching-adjusted GARNET endometrioid cohort from MAIC Scenario 1) standard parametric models

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Standard parametric models				
Generalised gamma[b]	[redacted]	2	[redacted]	5
Weibull	[redacted]	6	[redacted]	6
Gamma	[redacted]	7	[redacted]	7
Exponential	[redacted]	3	[redacted]	1
Log-logistic	[redacted]	5	[redacted]	4
Lognormal	[redacted]	1	[redacted]	2
Gompertz	[redacted]	4	[redacted]	3

Footnotes: [a] A lower AIC or BIC value represents a better goodness of fit. [b] The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; MAIC: matching-adjusted indirect comparison; OS: overall survival.

Figure 31: Dostarlimab OS extrapolations (matching-adjusted GARNET endometrioid cohort from MAIC Scenario 1) – up to 5 years – prior to treatment waning

[redacted]

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: OS: overall survival; MAIC: matching-adjusted indirect comparison.

Figure 32: Dostarlimab OS extrapolations (matching-adjusted GARNET endometrioid cohort from MAIC Scenario 1) – up to 40 years – prior to treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: OS: overall survival; MAIC: matching-adjusted indirect comparison.

Figure 33: Dostarlimab OS extrapolations (matching-adjusted GARNET endometrioid cohort from MAIC Scenario 1) – up to 5 years – post treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: OS: overall survival; MAIC: matching-adjusted indirect comparison.

Figure 34: Dostarlimab OS extrapolations (matching-adjusted GARNET endometrioid cohort from MAIC Scenario 1) – up to 40 years – post treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma,
Abbreviations: OS: overall survival; MAIC: matching-adjusted indirect comparison.

Appendix 2

Modified Assessment Schedule Matching ITC between PFS in GARNET and ZoptEC

As noted in the CS Document B, it was not considered possible to use IPTW to estimate a HR for PFS between dostarlimab and doxorubicin, due to differences in the definition of PFS and the timepoints of tumour assessments between GARNET and ZoptEC.[22-24] PFS was defined from the date of the first dose of dostarlimab in GARNET, but defined as the time elapsed from randomisation in ZoptEC.[22-24] Patients were assessed every six weeks for disease progression starting from Week 12 in GARNET; conversely, patients were re-evaluated for response every nine weeks in ZoptEC.[22-24]

The Company has now explored a modified assessment-scheduled matching analysis between PFS in GARNET and ZoptEC, to provide a more robust scenario versus doxorubicin (given that otherwise, it is necessary to use the PFS HR versus the published Makker et al. 2013[21] study as a proxy, which is associated with substantial uncertainty). The assessment schedules were matched using the methodology detailed by Kapentenakis et al. (2019).[25]

Due to violation of the PH assumption, the ratio between PFS for dostarlimab and doxorubicin was derived using an accelerated failure time model with Weibull distributions, summarised in Table 24.

Table 24: Summary of modified assessment-schedule matching analysis between PFS for dostarlimab (GARNET) and doxorubicin (ZoptEC)

	N	Hazard ratio (Dostarlimab/ doxorubicin)	95% CI	StdErr	p_value
AFT model (Weibull distributions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AFT: accelerated failure time; CI: confidence interval; PFS: progression-free survival; StdErr: standard error.

Survival analysis associated with the ZoptEC ITC

Dostarlimab PFS

Table 25: Summary of goodness-of-fit data for dostarlimab PFS (matching-adjusted GARNET population from modified assessment-schedule matching IPTW ITC versus doxorubicin in ZoptEC)

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Standard parametric models				
Generalised gamma	[redacted]	1	[redacted]	1
Weibull	[redacted]	5	[redacted]	5
Gamma	[redacted]	6	[redacted]	6
Exponential	[redacted]	7	[redacted]	7
Log-logistic	[redacted]	4	[redacted]	4
Lognormal[b]	[redacted]	3	[redacted]	3
Gompertz	[redacted]	2	[redacted]	2

Footnotes: [a] A lower AIC or BIC value represents a better goodness of fit. [b] The Company's preferred extrapolation is the lognormal.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; PFS: progression-free survival.

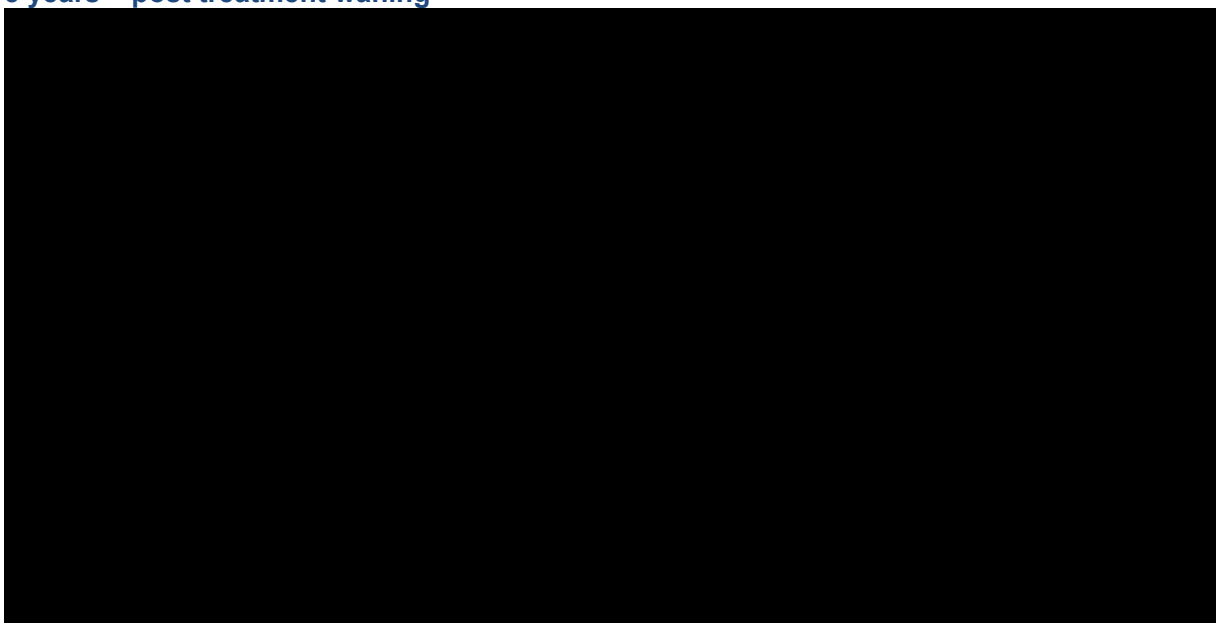
Figure 35: Dostarlimab PFS extrapolations - matching-adjusted GARNET population from modified assessment-schedule matching IPTW ITC versus doxorubicin in ZoptEC – up to 5 years – prior to treatment waning

Footnotes: The Company's preferred extrapolation is the lognormal.
Abbreviations: ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; PFS: progression-free survival.

Figure 36: Dostarlimab PFS extrapolations - matching-adjusted GARNET population from modified assessment-schedule matching IPTW ITC versus doxorubicin in ZoptEC – up to 40 years – prior to treatment waning

Footnotes: The Company's preferred extrapolation is the lognormal.
Abbreviations: ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; PFS: progression-free survival.

Figure 37: Dostarlimab PFS extrapolations - matching-adjusted GARNET population from modified assessment-schedule matching IPTW ITC versus doxorubicin in ZoptEC – up to 5 years – post treatment waning



Footnotes: The Company's preferred extrapolation is the lognormal.
Abbreviations: ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; PFS: progression-free survival.

Figure 38: Dostarlimab PFS extrapolations - matching-adjusted GARNET population from modified assessment-schedule matching IPTW ITC versus doxorubicin in ZoptEC – up to 40 years – post treatment waning

Footnotes: The Company's preferred extrapolation is the lognormal.
Abbreviations: ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; PFS: progression-free survival.

Doxorubicin PFS

Table 26: Summary of goodness-of-fit data for doxorubicin PFS (matching-adjusted ZoptEC population from modified assessment-schedule matching IPTW ITC versus dostarlimab in GARNET)

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Standard parametric models				
Generalised gamma	[redacted]	7	[redacted]	7
Weibull	[redacted]	3	[redacted]	2
Gamma	[redacted]	4	[redacted]	4
Exponential	[redacted]	5	[redacted]	5
Log-logistic[b]	[redacted]	1	[redacted]	1
Lognormal	[redacted]	6	[redacted]	6
Gompertz	[redacted]	2	[redacted]	3

Footnotes: [a] A lower AIC or BIC value represents a better goodness of fit. [b] The Company's preferred extrapolation is the log-logistic.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; PFS: progression-free survival.

Figure 39: Doxorubicin PFS extrapolations - matching-adjusted ZoptEC population from modified assessment-schedule matching IPTW ITC versus dostarlimab in GARNET – up to 5 years

Footnotes: The Company's preferred extrapolation is the log-logistic.
Abbreviations: ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; KM: Kaplan-Meier; PFS: progression-free survival; TTNT: time to next treatment.

Figure 40: Doxorubicin PFS extrapolations - matching-adjusted ZoptEC population from modified assessment-schedule matching IPTW ITC versus dostarlimab in GARNET – up to 40 years

Footnotes: The Company's preferred extrapolation is the log-logistic.
Abbreviations: ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; KM: Kaplan-Meier; PFS: progression-free survival; TTNT: time to next treatment.

Dostarlimab OS

Table 27: Summary of goodness-of-fit data for dostarlimab OS (matching-adjusted GARNET population from IPTW ITC versus doxorubicin in ZoptEC)

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Generalised gamma[b]	[redacted]	2	[redacted]	5
Weibull	[redacted]	6	[redacted]	6
Gamma	[redacted]	7	[redacted]	7
Exponential	[redacted]	3	[redacted]	1
Log-logistic	[redacted]	5	[redacted]	4
Lognormal	[redacted]	1	[redacted]	2
Gompertz	[redacted]	4	[redacted]	3

Footnotes: [a] A lower AIC or BIC value represents a better goodness of fit. [b] The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; OS: overall survival.

Figure 41: Dostarlimab OS extrapolations (matching-adjusted GARNET population based on IPTW ITC versus doxorubicin in ZoptEC) – up to 5 years – prior to treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; OS: overall survival.

Figure 42: Dostarlimab OS extrapolations (matching-adjusted GARNET population based on IPTW ITC versus doxorubicin in ZoptEC) – up to 40 years – prior to treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; OS: overall survival.

Figure 43: Dostarlimab OS extrapolations (matching-adjusted GARNET population based on IPTW ITC versus doxorubicin in ZoptEC) – up to 5 years – post treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; OS: overall survival.

Figure 44: Dostarlimab OS extrapolations (matching-adjusted GARNET population based on IPTW ITC versus doxorubicin in ZoptEC) – up to 40 years – post treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; OS: overall survival.

Doxorubicin OS

Table 28: Summary of goodness-of-fit data for doxorubicin OS (matching-adjusted ZoptEC population based on IPTW ITC versus dostarlimab in GARNET) standard parametric models

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Exponential	[redacted]	6	[redacted]	6

Weibull	[redacted]	5	[redacted]	5
Lognormal	[redacted]	3	[redacted]	2
Log-logistic[b]	[redacted]	1	[redacted]	1
Gamma	[redacted]	4	[redacted]	3
Gompertz	[redacted]	7	[redacted]	7
GenGamma	[redacted]	2	[redacted]	4

Footnotes: [a] A lower AIC or BIC value represents a better goodness of fit. [b] The Company's preferred extrapolation is the log-logistic.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Figure 45: Doxorubicin OS extrapolations (matching-adjusted ZoptEC population based on IPTW ITC versus dostarlimab in GARNET) – up to 5 years

Footnotes: The Company's preferred extrapolation is the log-logistic.
Abbreviations: ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; KM: Kaplan-Meier; OS: overall survival.

Figure 46: Doxorubicin OS extrapolations (matching-adjusted ZoptEC population based on IPTW ITC versus dostarlimab in GARNET) – up to 40 years

Footnotes: The Company's preferred extrapolation is the log-logistic.
Abbreviations: ITC: indirect treatment comparison; IPTW: inverse probability of treatment weighting; KM: Kaplan-Meier; OS: overall survival.

Summary of chosen extrapolations for the Scenario 10 between dostarlimab (GARNET) and doxorubicin (ZoptEC)

Table 29: Extrapolations for the scenario analysis between dostarlimab (GARNET) and doxorubicin (ZoptEC) – Scenario 10

	Dostarlimab	Doxorubicin
PFS	Lognormal	Log-logistic
OS	Generalised gamma	Log-logistic

Abbreviations: OS: overall survival; PFS: progression-free survival.

Appendix 3 Matching-adjusted dostarlimab OS data (derived from the MAIC versus the RWEQ population, Scenario 1)

Overall Survival

Dostarlimab – (matching-adjusted ITT population) – MAIC Scenario 1

Table 30: Summary of goodness-of-fit data for dostarlimab OS (GARNET ITT population) standard parametric models

Distribution	AIC[a]	AIC Rank	BIC[a]	BIC Rank
Standard parametric models				
Generalised gamma[b]	[redacted]	1	[redacted]	5
Weibull	[redacted]	6	[redacted]	6
Gamma	[redacted]	7	[redacted]	7
Exponential	[redacted]	3	[redacted]	1
Log-logistic	[redacted]	4	[redacted]	3
Lognormal	[redacted]	2	[redacted]	2
Gompertz	[redacted]	5	[redacted]	4

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit. [b] The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; ToT: time on treatment.

Figure 47: Dostarlimab OS extrapolations (matching-adjusted GARNET population based on the MAIC versus the RWEQ, Scenario 1) – up to 5 years – prior to treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: OS: overall survival; RWE: real-world evidence; RWEQ: real-world equivalent; MAIC: matching adjusted indirect comparison.

Figure 48: Dostarlimab OS extrapolations (matching-adjusted GARNET population based on the MAIC versus the RWEQ, Scenario 1) – up to 40 years – prior to treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: OS: overall survival; RWE: real-world evidence; RWEQ: real-world equivalent; MAIC: matching adjusted indirect comparison.

Figure 49: Dostarlimab OS extrapolations (matching-adjusted GARNET population based on the MAIC versus the RWEQ, Scenario 1) – up to 5 years – post treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: OS: overall survival; RWE: real-world evidence; RWEQ: real-world equivalent; MAIC: matching adjusted indirect comparison.

Figure 50: Dostarlimab OS extrapolations (matching-adjusted GARNET population based on the MAIC versus the RWEQ, Scenario 1) – up to 40 years – post treatment waning

Footnotes: The Company's preferred extrapolation is the Generalised gamma.
Abbreviations: OS: overall survival; RWE: real-world evidence; RWEQ: real-world equivalent; MAIC: matching adjusted indirect comparison.

Appendix 4 Company revised treatment waning methodology

The ERG's treatment waning methodology includes one phase of treatment waning and assumes that all patients discontinue treatment at the end of [redacted], and applies treatment waning accordingly.

The Company's revised treatment waning methodology includes four different phases of treatment waning:

- **Treatment Waning Phase 1**: Assumes that patients discontinue treatment at the end of [redacted], treatment waning begins after an offset of [redacted], and ends at the end of [redacted]

Treatment Waning Phase 2: Assumes that patients discontinue treatment at the end of [redacted], treatment waning begins after an offset of [redacted], and ends at the end of [redacted]**Treatment Waning Phase 3**: Assumes that patients discontinue treatment at the end of [redacted], treatment waning begins after an offset of [redacted], and ends at the end of [redacted]**Treatment Waning Phase 4**: Assumes that patients discontinue treatment at the end of [redacted], treatment waning begins after an offset of [redacted], and ends at the end of [redacted]

The model divides the dostarlimab ToT curve into four distinct groups, to determine the proportions of patients allocated to each of the treatment waning phases. The proportions of patients allocated to each group are calculated by rounding down ToT to the nearest whole year completed:

  - Group 1: Patients who discontinue treatment up to the end of [redacted]*Patients Off Treatment at* [redacted] *(first cycle of* [redacted]*)*
  - Group 2: Patients who discontinue treatment up to the end of [redacted]*Patients Off Treatment at* [redacted] *(first cycle of* [redacted]*) minus Patients Off Treatment at* [redacted] *(first cycle of* [redacted]*)*
  - Group 3: Patients who discontinue treatment up to the end of [redacted]*Patients Off Treatment at* [redacted] *(last cycle of* [redacted]*) minus Patients Off Treatment at* [redacted] *(first cycle of* [redacted]*)*

- Group 4: Patients who remain on treatment until the last cycle of [redacted] (and only discontinue because [redacted])
  - *Patients On Treatment at* [redacted] *(last cycle of* [redacted]*)*

For example, patients who discontinue dostarlimab after [redacted] would be allocated to Group 1, and treatment waning would be applied as if these patients discontinued at the end of Year 2.

Patients are only allocated into the next treatment waning phase once they have remained on treatment for the next full year. So, patients who discontinue after [redacted] are rounded down, and allocated to Group 1. But patients who discontinue at [redacted] would be allocated to Group 2, because they completed a full additional year of treatment with dostarlimab.

In the Company's base case, the proportions of patients in each of these groups is detailed in Table 31.

Table 31: Proportion of patients in each treatment waning group

Group 1	Group 2	Group 3	Group 4
[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] The proportion of patients in Group 1 is calculated as the patients who discontinue up to the end of [redacted] ([redacted]%), as well as the patients who discontinue treatment up to the end of [redacted] ([redacted]%).

For patients in Group 1, treatment waning is applied in an identical manner to the ERG's approach. These patients are all assumed to discontinue treatment at the end of [redacted]. Treatment waning begins after an offset of [redacted] and lasts for [redacted]. At the end of [redacted], all patients in Group 1 have a hazard of death equal to the hazard of death for patients who initially received treatment with current clinical management. This represents a conservative assumption, because some of these patients continue to receive dostarlimab beyond [redacted]. Nevertheless, this is made as a simplifying assumption to ensure that the Company's approach remains conservative.

Patients in Group 2 and Group 3 are assumed to discontinue treatment at the end of [redacted] and at the end of [redacted], respectively. Treatment waning begins after an offset of [redacted] and lasts for [redacted]. At the end of [redacted] and [redacted], all patients in Group 2 and Group 3, respectively, have a hazard of death equal to the hazard of death for patients who initially received treatment with current clinical management. This is conservative, because all of the patients in this group receive dostarlimab beyond the end of [redacted] and [redacted], respectively, but are assumed to discontinue at the end of [redacted] and [redacted] as a simplifying assumption.

Patients in Group 4 are predicted to remain on treatment until the end of [redacted], and therefore, are assumed to discontinue treatment at the end of [redacted] for the purposes of applying treatment waning. At the end of [redacted], all patients in Group 4 have a hazard of death equal to the hazard of death for patients who initially received treatment with current clinical management.

For each group, a treatment waning percentage modifier is applied, in line with the ERG's approach – before treatment waning, this modifier is 0%, and once treatment waning has finished, this modifier is 100%. During each model cycle, a weighted average of the four treatment waning modifiers, based on the proportions of patients in each group, is calculated – the resulting weighting average is then used as the Company's overall treatment waning modifier.

Appendix 5 Clinical efficacy results for cost-effectiveness scenarios versus individual treatments

Table 32: The Company's chosen OS and PFS extrapolations for individual treatment scenario analyses based on the RWEQ

Comparator	Chosen comparator PFS extrapolation	Chosen comparator OS extrapolation	Incremental LYs gained for dostarlimab versus comparator (Waning dostarlimab to overall RWEQ curve)	Incremental LYs gained for dostarlimab versus comparator (Waning dostarlimab to individual treatment RWEQ curve)
Carboplatin plus paclitaxel	Log-logistic	Log-logistic	[redacted]	[redacted]
Carboplatin monotherapy	Log-logistic	Log-logistic	[redacted]	[redacted]
PLD monotherapy	Log-logistic	Log-logistic	[redacted]	[redacted]
Paclitaxel monotherapy	Log-logistic	Log-logistic	[redacted]	[redacted]
Carboplatin plus PLD	Log-logistic	Log-logistic	[redacted]	[redacted]

Abbreviations: LYs: life years; OS: overall survival; PLD: pegylated liposomal doxorubicin; PFS: progression-free survival; RWEQ: real-world equivalent.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **16 September**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency and current treatment options	
About you	
1. Your name	**Dr Susana Banerjee**
2. Name of organisation	**The Royal Marsden NHS Foundation Trust**
3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	✓☐ an employee or representative of a healthcare professional organisation that represents clinicians? ✓ ☐ a specialist in the treatment of people with advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency? ✓ ☐ a specialist in the clinical evidence base for advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your	☐ ✓ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ I did not write the submission
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improve survival: Overall Survival and Progression-free survival (delay progression) Improve chances of response (amount of tumour shrinkage) and duration of response Improve Quality of Life
9. What do you consider a clinically significant treatment	Given the response rate to conventional chemotherapy for dMMR (mismatch repair deficient) recurrent endometrial cancer (prior platinum therapy) is 12.3% (median duration 4.1 months), PFS 3.7 months, OS 8.6

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	months (Makker et al IGCS 2021) I would consider 30% as meaningful response rate by RECIST. Ie 30% of patients having 30% or more tumour shrinkage
10. In your view, is there an unmet need for patients and healthcare professionals in advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency?	Yes. Very much so. Up until now, there has been limited treatment options outside of clinical trials for women with recurrent/advanced endometrial cancer including those with dMMR/MSI-H tumours. Pembrolizumab (PD-1 inhibitor) gained FDA approval in 2017 based on early phase trials for patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. This tumour agnostic indication includes endometrial cancer. However, this is not available for NHS patients. NHS patients with dMMR/MSI-H recurrent/endometrial endometrial cancer need to have access to PD-1 inhibitors such as Dostarlimab.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Treatment outside of clinical trials, is unfortunately not personalised for women with dMMR/MSI-H endometrial cancer because there is no NICE or CDF approved (outside of COVID-19 temporary access) PD-1/L1 inhibitor. Patients therefore receive chemotherapy or ant-oestrogen/hormonal therapy as standard of care. During COVID-19, patients with DMMR/MSI-H could access nivolumab. I am aware of NHS patients, including those under my care, who have accessed this PD-1 inhibitor and had better outcomes than expected with chemotherapy. To my knowledge, there is more published evidence of efficacy and tolerability (including more patients) in endometrial cancer for the PD-1 inhibitor, dostarlimab.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. BGCS guidelines, ESGO-ESTRO Endometrial Cancer Guidelines.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Given the lack of substantial progress till now in systemic treatment of endometrial cancer, there may be differences of opinion within the NHS. However, there is universal recognition and agreement that PD-1 inhibitors such as dostarlimab have shown substantial efficacy in early phase trials compared to outcomes we have seen for patients in clinics receiving chemotherapy.
• What impact would the technology have on the current pathway of care?	The beneficial impact would be considerable. From practical perspective, MMR testing (or microsatellite instability status) would be necessary as part of routine care to direct personalisation of treatment to access immunotherapy. This is already happening in many cancer centres (pathology departments test this for other cancers such as colorectal). For example, this is routine practice at the hospital I work in.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This treatment will fit into the current treatment pathway when considering options for patients.
• How does healthcare resource use differ between the technology and current care?	Need for biomarker (immunohistochemistry for MMR) testing to identify patients.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care specialist cancer clinics

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	MMR testing (which as stated before is occurring in NHS centres more widely now)
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Very much so.
• Do you expect the technology to increase length of life more than current care?	Although final overall survival results are not available and the GARNET trial is non-randomised, given the results so far and from my clinical experience as an investigator in this trial and use of PD-1 inhibitors in clinical practice, I expect length of life to be longer compared to current care.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. By virtue, of less toxicities than some chemotherapy agents, delaying progression events and therefore disease-related complications
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes. dMMR /MSI-H endeomtrial cancer patients are most likely to benefit
The use of the technology	

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Different, however many oncologist treat more than 1 cancer and will have experience of IO which is sOC in other cancers eg lung, melanoma Monitoring and administration similar to chemotherapy initially and then less frequent (6 weekly). Patients in my experience are willing and keen to access immunotherapy to avoid chemotherapy given their knowledge of current outcomes with chemotherapy/hormonal therapy yet associated with toxicities eg hair loss, increase sepsis
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Stop for toxicities, if treatment not working (cancer progression) Scans and clinical assessments which would occur on any other treatment
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in	No

the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes 1st NICE or CDF approved (outside of COVID-19 temporary access) immunotherapy for endometrial cancer. This will allow personalisation according to biology and greatest liklihood of benefit for individual patients
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes. Liklihood of response which is low with current treatment, duration of response, Progression-free survival and hopefully (likely) overall survival.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are recognised class effect of immunotherapy. Cancer Clinicians increasingly familiar given the apporvals in other tumour types. Thyroid function changes (most frequent) and is treatable.. More significant, potentially life-changing side effects are rare. It is important to note that standard of care chemotherapy can also cause side effects which can be life-threatening such as neutropenic sepsis

Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes The GARNET trial was open in the UK and recruited women with endometrial cancer.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS, OS, response, response duration, toxicity and HRQoL These outcomes are all measured in GARNET trial (primary and secondary endpoints of this phase I, non-randomised)) progression-free survival (PFS) at time points and median, OS have been presented at month 12 and 24. (trial follow up ongoing)
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	OS at specific timepoints are helpful indicators when considering patient treatment decisions in practice. However, in the non-randomised trial setting, there are limitations.
• Are there any adverse effects that were not apparent in clinical trials but	No

have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not beyond those presented at congresses in 2021.
23. How do data on real-world experience compare with the trial data?	A wealth of Real-world experience is lacking in endometrial cancer- in particular dMMR/MSI-H subtype. This is a challenge in such an evaluation. Retrospective hospital series or healthcare system databases have limitations. NHS data sets are unlikely to have comprehensive biomarker (dMMR/MSI-H) details integrated yet.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access to MMR/MSI-H testing – need to ensure all geographical areas can access and offer to all patients irrespective of age and ethnicity, language.
24b. Consider whether these issues are different from issues with current care and why.	Similar issues are relevant when introducing any new biomarker test to guide treatment decision making. This will be the first time in endometrial cancer

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: The patient population specified in marketing authorisation and addressed in the company submission (CS) is narrower that what is specified in the final scope	Final scope issued by NICE states previously treated for recurrent or advanced endometrial cancer. Company submission states prior platinum-based regimen. I agree that first line systemic therapy in standard care is platinum-based. With the wording by NICE, there is the possibility that chemo-naïve patients with recurrent or advanced disease could receive dostarlimab. These patients were not included in GARNET and are not in keeping with the EMA marketing authorisation granted. The efficacy compared to standard treatment options is not known yet for chemo-naïve patients.
Key issue 2: Patients with advanced disease and with recurrent disease are potentially two distinct populations, but they were identified in different ways between the	The majority of endometrial cancer trials include both recurrent and advanced disease and to date, have not always separated these groups out. Recurrent disease could be local and therefore non-systemic therapy (ie chemotherapy or hormonal therapy) is an option (eg radiotherapy or surgery). Systemic therapy is usually an option considered for patients with disease not amenable to local treatment. Given the criteria in the GARNET trial and company submission for

GARNET trial for dostarlimab and the GARNET-like Real World EQuivalent (RWEQ) cohort	prior platinum, I don't believe the potential differences in outcome between two populations is substantial.
Key issue 3: Overall the GARNET trial data were fairly immature and may not be sufficient to provide reliable effectiveness and cost-effectiveness estimates	This is an intrinsic issue of all newly reported trials of novel therapies. In particular, non-randomised early phase trials. It is a balance of waiting for long term follow-up for outcomes such as survival and access to the latest treatments which have shown higher efficacy in some endpoints (response, duration of response) in a population with a significant unmet need. This is the case for recurrent/advanced endometrial cancer where current treatments have limited efficacy. Furthermore, the efficacy reported in GARNET is consistent with the scientific rationale of immunotherapy approaches in dMMR/MSI-H tumours (seen in other tumour types).
Key issue 4: There are uncertainties over the magnitude of the benefit of dostarlimab relative to comparators due to the single-arm design of the GARNET trial and lack of suitable data for comparator treatments	Reported prospective trials specifically in dMMR endometrial cancer are limited. The best example to my knowledge is the Phase 3, randomised trial study309/MK-775 of Lenvatinib+pembrolizumab vs standard of care. This subgroup analysis of dMMR patients (Makker et al I am a co-author) was presented in August 2021 at IGCS. Patients had advanced/metastatic or recurrent endometrial cancer and prior platinum-based therapy. The PFS in the comparator arm (n=65) in the dMMR population was 3.7 months (3.1-4.4 95% CI) The OS in the comparator arm in the dMMR population was 8.6 months (5.5-12.9 95% CI) Response rate 12.3% median duration 4.1 months

	The response rate (44.8%), duration of response (median not reached), PFS and OS to date seen in GARNET is greater than above.
Key issue 5: GARNET trial population and RWEQ cohort may have fundamental differences that cannot be easily adjusted statistically	Several differences have been highlighted in the reports. In my view, the most notable is that the RWEQ will include patients that are biomarker positive and negative ie dMMR and pMMR. However, to my knowledge, given that MMR testing is relatively recent in practice, it will be a challenge to have robust, comprehensive retrospective data on standard of care according to MMR status.
Key issue 6: Model errors	The main difference in the modelling stems from waning effect assumptions. It is a clinically reasonable assumption that a treatment effect from dostarlimab is maintained for patient progression-free at the point treatment waning is assumed to end.
Key issue 7: Dostarlimab overall survival (OS) elicitation exercise and choice of OS curve	I am not an expert on modelling/choice of curve
Key issue 8: RWEQ OS elicitation exercise and choice of OS curve	This is limited as highlighted earlier, given patients without dMMR/MSI-H are inevitably included. I am not an expert on modelling/choice of curve
Key issue 9: Dostarlimab time to treatment discontinuation (TTD) elicitation exercise and treatment discontinuations	I am not an expert on modelling/choice of curve

Key issue 10: Dostarlimab choice of TTD curve	I am not an expert on modelling/choice of curve
Key issue 11: Censoring and the possibility of informative censoring	This is a limitation of non-randomised trials
Key issue 12: Reliability of comparing GARNET with the RWEQ	This is acceptable given the limited alternatives.
Are there any important issues that have been missed in ERG report?	No
Does prognosis differ between people with advanced endometrial cancer and those with recurrent endometrial cancer?	To my knowledge not fully known. These groups are usually combined in trials
What would be the expected overall survival time for people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency from the start of next-line dostarlimab?	Based on comparator arm (standard of care chemotherapy doxorubicin or paclitaxel) of study 309/MK-775, overall survival 8.6 months In GARNET, 57% alive at 24 months

Are the patient characteristics in the GARNET ITT trial (Table 10, ERG report) representative of patient characteristics for people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency?	Yes
Are the patient characteristics in the GARNET-like UK RWE (RWEQ) cohort (Table 10, ERG report) representative of patient characteristics for people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency?	The RWEQ is representative of dMMR and pMMR. To date, there is no difference in current standard of care choices. It is possible that more dMMR may receive hormonal therapy in practice given endometrioid histology is often ER positive. However, if disease burden is moderate/high and rapidly progressing, then chemotherapy would be used.
Are the patient characteristics in the ZoptEC (Table 40, company submission, appendices) representative of patient characteristics for people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency?	Yes- however limitations as above given ZoptEC was not biomarker specified. So pMMR tumours were also included (higher proportion of serous in ZoptEC)
What proportion of people with previously treated advanced or recurrent endometrial cancer with high	There is wide range from experts reflecting the lack of information to answer this question specifically for patients with dMMR/MSI-H. This is because PD-1 inhibitors are a new therapy for endometrial cancer and therefore

microsatellite instability or mismatch repair deficiency would be expected to be progression-free at 3,5,10,15 and 20 years following treatment with dostarlimab?	long term experience is physically not available.
What proportion of people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency would be expected to be alive at 3,5,10,15 and 20 years following treatment with dostarlimab?	There is wide range from experts reflecting the lack of information to answer this question specifically for patients with dMMR/MSI-H. This is because PD-1 inhibitors are a new therapy for endometrial cancer and therefore long term experience is physically not available.
What proportion of people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency would be expected to remain on treatment with dostarlimab after 1, 2,3, 4, and 5 years?	There is wide range from experts reflecting the lack of information to answer this question specifically for patients with dMMR/MSI-H. This is because PD-1 inhibitors are a new therapy for endometrial cancer and therefore long term experience is physically not available.
Due to treatment waning, what would you expect the treatment efficacy to decrease by in people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency at after 1, 2,3, 4, and 5 years after dostarlimab cessation?	I do not expect the treatment efficacy to substantially drop off. Some patients in my clinical experience and in trials, have stopped PD-1 inhibitor treatment in the absence of disease progression (eg blood tests/toxicity and trial criteria, funding) and continue to remain disease progression free, alive and well 2-3 years later. It is too early to speculate whether there will be a treatment waning effect in endometrial cancer as this is a new treatment modality in this disease. My instinct is that it is entirely feasible that treatment till progression may not be

	required as there may be no/limited detriment to efficacy following 2-3 years of treatment for example. The first line ENGOT-EN6/NSGO-RUBY (chemotherapy naïve trial) currently ongoing has dostarlimab for up to 3 years in the absence of progression.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- There is a substantial unmet need for the treatment of women with recurrent and advanced endometrial cancer post platinum-based chemotherapy with current NHS options outside of clinical trials having relatively low response rates, poor PFS and overall survival of around 1 year.
- The GARNET trial has the largest cohort to date of women with dMMR/MSI-H endometrial cancer and the efficacy to date has led to EMA marketing authorisation given the unmet need.
- Although a non-randomised, phase I trial, the activity seen with dostarlimab in dMMR/MSI-H endometrial cancer is the most promising to date for this group of women showing higher efficacy than available treatments in the NHS.
- The availability in the NHS of dostarlimab would represent the first biomarker-driven, personalised treatment for women with dMMR/MSI-H recurrent/advanced endometrial cancer- a significant step forward
- Further follow- up within GARNET and real-world data specifically in dMMR/MSI-H will confirm/establish long term outcomes

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Clinical expert statement & technical engagement response form

Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

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Please return this form by **5pm** on **16 September**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency and current treatment options	
About you	
1. Your name	**Andrew Clamp**
2. Name of organisation	**The Christie NHS Foundation Trust (nominated by GSK)**
3. Job title or position	**Consultant and Honorary Senior Lecturer in Medical Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency? ☐ a specialist in the clinical evidence base for advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
The aim of treatment for advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The primary aims of treatment are to prevent disease progression, prolong survival and maintain/ improve quality of life.
9. What do you consider a clinically significant treatment response? (For example, a	Although radiological assessments of disease response using RECIST criteria are reported in clinical trials of anti-cancer therapies, stable disease can also have important clinical benefits for patients and be associated with improvement in disease-related symptoms. Progression-free survival is often a more important marker of treatment benefit.

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency?	Treatment options for this population are extremely limited and there is no defined standard-of-care therapy after failure of platinum-based chemotherapy. Response rates to second-line treatments are low and survival is less than a year. There is a huge unmet need for novel efficacious targeted therapies in mismatch-repair deficient advanced/ recurrent endometrial cancer.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Uterine cancer is now the fourth most common cancer in females in the UK. Incidence in the UK has increased by around 55% since the 1990s with ~9,400 women diagnosed per year in 2015-2017. While many patients are diagnosed with early stage disease (FIGO stage I and II) that is often curable with surgery with or without adjuvant treatment, about 20 % of these patients experience disease relapse, and 25-30 % of women present with FIGO stage III-IV disease. Uterine cancer accounted for 2,409 deaths in the UK 2018. For those women requiring systemic treatment for advanced/ recurrent endometrial cancer, carboplatin-paclitaxel is the established standard-of-care with response rates of 50-60% reported in clinical trials. However, median survival is disappointing low with most trials reporting overall survival figures of less than 2 years. In a minority of women with low grade hormone receptor positive recurrent disease, endocrine therapy, generally with a progestagen can be effective alternative treatment approach to chemotherapy. No defined standard for second-line therapy exists however, and phase II evaluations of multiple cytotoxic agents have reported response rates in this setting of approximately 10 % with median PFS and OS of 3 and 10 months respectively (Fleming et al 2015). There is therefore an urgent need to define more effective treatment strategies for

	recurrent/ progressive endometrial cancer, and to evaluate the activity of targeted agents in this patient group. In the absence of a defined second-line or later standard treatment, many centres are utilising weekly paclitaxel in this setting as it is well-tolerated, has little negative impact on Quality of Life and is supported by phase II data (Homesley et al 2008). Alternative treatment options include doxorubicin, pegylated liposomal doxorubicin or the consideration of platinum rechallenge in women where a durable response occurred to first-line treatment.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The most commonly used guidelines are; BGCS (2017- undergoing update), ESGO-ESTRO-ESP (December 2020), ESMO (2016). None of these define a second-line standard-of-care treatment for recurrent/advanced endometrial cancer. The ESGO-ESTRO-ESP guidelines consider appropriate options to be platinum rechallenge if there is a prolonged interval from first-line treatment or the use of weekly paclitaxel or anthracyclines (including pegylated liposomal doxorubicin). All guidelines actively encourage entry in to open clinical trials if these are available.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Although there is not a defined standard-of-care second line therapy, most centres would consider second-line treatments with the regimens recommended above alongside supportive care.
• What impact would the technology have on the current pathway of care?	This would provide a new, molecularly-defined standard-of-care second-line treatment with substantially improved efficacy for women with mismatch-repair deficient advanced/recurrent endometrial cancer.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Dostarlimab would be used after failure of platinum-based chemotherapy for women with mismatch-repair deficient advanced/recurrent endometrial cancer instead of currently used second-line chemotherapy options. This would be the same patient group as was recruited to the GARNET trial.
• How does healthcare	There would be little if any increase in healthcare resource use associated with a switch from second-line

resource use differ between the technology and current care?	chemotherapy to dostarlimab. Although the treatment duration for dostarlimab is longer, the frequency of infusions is reduced compared to the most commonly used current treatment option (weekly paclitaxel). MMR immunohistochemistry is now a NICE-recommended evaluation performed at diagnosis for endometrial cancer so there will be minimal resource impact required to identify the biomarker-selected patient group who would benefit from dostarlimab.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This treatment would be administered in secondary care overseen by medical/ clinical oncologists experienced in the management of advanced/recurrent endometrial cancer.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As immunotherapy is an established treatment modality for many other cancer types, the infrastructure and clinical expertise is already in place to manage women with endometrial cancer treated with dostarlimab.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The results of the GARNET trial demonstrate that dostarlimab will provide a substantial benefit to women with recurrent MMR deficient endometrial cancer after failure of platinum-based chemotherapy. In the 105 evaluable patients treated with dostarlimab, a response rate of 45% was reported, Notably these responses were remarkably durable with 80% of responders still experiencing a response at 18 months. This duration of response is rarely seen with second-line chemotherapy. 49% of the intention to treat population (129 patients) was also progression-free 12 months after commencing dostarlimab and 58% were alive at 2 years.
• Do you expect the technology to increase length of life more than current care?	Yes, the durability of treatment responses to dostarlimab and the PFS and OS results reported in the GARNET trial means that I think it is very likely that dostarlimab will increase survival compared to current standard-of –care treatment options. Although the lack of a standard-of-care control arm in the GARNET trial makes assessment of the magnitude of benefit more difficult, data from the RWE cohort, and the control arm of the ZoptEC trial give very similar median OS figures on 10.3 and 10.8 months respectively with chemotherapy treatment. This compares to a median OS of >18.4 months in the GARNET trial.

	In addition, the primary analysis of the phase III KEYNOTE-775 trial was presented at the SGO annual meeting this year (Makker et al 2021). This trial randomised 827 women with advanced/metastatic/ recurrent endometrial cancer which had progressed after platinum-based chemotherapy to an experimental arm of lenvatinib-pembrolizumab or a control arm of standard-of-care chemotherapy(weekly paclitaxel or doxorubicin). Median OS in the control arm was 11.4 months. This confirms that survival is less than 12 months for women with advanced/recurrent endometrial cancer after failure of platinum-based chemotherapy receiving current standard-of-care treatments.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Although some women receiving dostarlimab will experience immune-related adverse events that might reduce quality-of-life. the incidence of these was low in the GARNET trial (13% treatment-related G3 AEs) and less than 5% of women discontinued treatment because of these. In contrast the incidence of significant toxicity from standard chemotherapy is substantially higher. The substantially higher response and disease control rates with dostarlimab compared to chemotherapy will also be associated with better control of disease –related symptoms that will improve quality-of-life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This appraisal is assessing the effectiveness of dostarlimab in a biomarker-selected population (women with MMR-deficient recurrent endometrial cancer). Although limited efficacy has been reported in women with MMR-profiicient endometrial cancer, this group is not included in this appraisal.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	Many oncologists and all specialist oncology centres are already familiar with the use of immunotherapy in the treatment of other malignancies. This means that treatment protocols will already be in place for the delivery of these drugs and the management of their toxicities. Given the routine intravenous administration of dostarlimab and the small number of patients who would be eligible at each centre, there are unlikely to be any significant capacity or resource implications,

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Although initially, many clinicians would treat patients until the development of disease progression or significant treatment-related toxicity, as they become familiar with the use of immunotherapy they may become confident in stopping dostarlimab treatment after a pre-specified treatment duration in those patients who have achieved a complete or deep partial response. Extrapolating from other tumour types where immunotherapy is much more established, this treatment duration is likely to be around 2 years. This would depend on the opportunity to retreat women whose disease subsequently progresses. Of note many trials evauating pembrolizumab (another anti-PD1monoclonal antibody) in metastatic disease now specify a maximum treatment duration of 35 cycles (approximately 2 years).
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
18. Do you consider the technology to be innovative in its	Yes. This is the first novel biomarker-directed therapy to be licensed in recurrent endometrial cancer. The high disease control rates and durable responses have the potential to changes the landscape for the treatment of MMRd

potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	recurrent endometrial cancer and offer women with this condition the potential for long-lasting control of their disease which is not achievable with current treatment options.
• Is the technology a 'step-change' in the management of the condition?	Yes- dostarlimab for the reasons discussed above is a substantial step-change for the treatment of women with MMRd advanced/ recurrent endometrial cancer after failure of platinum-based chemotherapy.
• Does the use of the technology address any particular unmet need of the patient population?	Yes
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Although some women receiving dostarlimab will experience immune-related adverse events that might reduce quality-of-life. The incidence of these was low in the GARNET trial (13% treatment-related G3 AEs) and less than 5% of women discontinued treatment because of these. All specialist onocology centres have guidelines for the recognition and management of toxicities associated with PD-1/PD-L1 inhibitors that will enable rapid identification and treatment of these side-effects.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Dostarlimab would be considered as a treatment option only in MMRd endometrial cancer after failure of platinum-based chemotherapy.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes reported in the GARNET trial are the overall response rate and in particular, the duration of response. 45% of women with MMRd advanced/recurrent endometrial cancer experienced a complete or partial response after dostarlimab therapy and 89% of these were still benefitting from a disease response after a median follow-up of 16.3 months resulting in a flattening of the progression-free survival Kaplan-Meier curves. This meant that nearly 40% of women with MMRd advanced/recurrent endometrial cancer treated with dostarlimab were progression-free at 2 years.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

23. How do data on real-world experience compare with the trial data?	NA
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.
24b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: The patient population specified in marketing authorisation and addressed in the company submission (CS) is narrower that what is specified in the final scope	
Key issue 2: Patients with advanced disease and with recurrent disease are potentially two distinct populations, but they were identified in different ways between the GARNET trial for dostarlimab and the GARNET-like Real World EQuivalent (RWEQ) cohort	
Key issue 3: Overall the GARNET trial data were fairly immature and may not be sufficient to provide reliable	

effectiveness and cost-effectiveness estimates	
Key issue 4: There are uncertainties over the magnitude of the benefit of dostarlimab relative to comparators due to the single-arm design of the GARNET trial and lack of suitable data for comparator treatments	
Key issue 5: GARNET trial population and RWEQ cohort may have fundamental differences that cannot be easily adjusted statistically	
Key issue 6: Model errors	
Key issue 7: Dostarlimab overall survival (OS) elicitation exercise and choice of OS curve	
Key issue 8: RWEQ OS elicitation exercise and choice of OS curve	
Key issue 9: Dostarlimab time to treatment discontinuation (TTD) elicitation exercise and treatment discontinuations	

Key issue 10: Dostarlimab choice of TTD curve	
Key issue 11: Censoring and the possibility of informative censoring	
Key issue 12: Reliability of comparing GARNET with the RWEQ	
Are there any important issues that have been missed in ERG report?	
Does prognosis differ between people with advanced endometrial cancer and those with recurrent endometrial cancer?	The inclusion of women with both advanced and recurrent endometrial cancer in clinical trials of novel treatments is universally accepted. This is because those women with advanced disease who enter trials such as GARNET, have persisting measurable sites of disease that are not amenable to surgical resection or radical radiotherapy regimens. As such, they have incurable disease and will have similar prognoses to those women with recurrent disease. In the GARNET trial, it should also be noted that all women entering the trial had also failed treatment with first-line platinum-based chemotherapy.
What would be the expected overall survival time for people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or	There is no robust peer-reviewed literature available on the survival of women with MMRd endometrial cancer from the time of diagnosis of incurable advanced/ recurrent disease with standard-of-care treatment. This is because until very recently, MMR status was not evaluated in endometrial cancer unless there was a strong family history suggestive of Lynch

mismatch repair deficiency from the start of next-line dostarlimab?	Syndrome. In the last 12 months, NICE guidance has been issued which recommends that MMR status is determined in all newly diagnosed case of endometrial cancer but it will be several years before survival analyses on the basis of MMR status will be able to be conducted. My best estimate is that median OS is likely to be similar amongst all women with previously treated advanced/ recurrent endometrial cancer after failure of platinum-based chemotherapy who are treated with current standard-of-care treatments, irrespective of MMR status. Of note, a retrospective single centre analysis of response to first-line platinum-chemotherapy in MSI-H metastatic endometrial cancer was presented in poster format at the ESMO Annual meeting last week (Colomba et al Abstract No 801P https://doi.org/10.1016/j.annonc.2021.08.1244). This included 78 evaluable patients. All received platinum-doublet chemotherapy (88% carboplatin-paclitaxel). 88% had endometrioid histology and 6% serous. Overall response rate was 50% with a median PFS of 7.8months. These efficacy figures are similar to those reported in phase II/III trials of carboplatin-paclitaxel in metastatic endometrial cancer supporting the idea that MMRd/MSI-H endometrial cancer does not respond differently to standard-of-care chemotherapy. Interestingly, median OS was 3.8 years in this cohort which is higher than reported in the published literature. This probably reflects the fact that 60% of patients in this cohort received immune checkpoint inhibitors after progression on chemotherapy suggesting that drugs like dostarlimab are having a positive impact on OS.
Are the patient characteristics in the GARNET ITT trial (Table 10, ERG report) representative of patient characteristics for people with previously treated advanced or recurrent endometrial cancer with high microsatellite	Yes. Although this group is somewhat younger that the whole group of women with previously, treated MMRd advanced/ recurrent endometrial cancer it is representative of the patient population who would be eligible for dostarlimab if this TA is approved given that an ECOG PS of 0-1 is required for treatment.

instability or mismatch repair deficiency?	
Are the patient characteristics in the GARNET-like UK RWE (RWEQ) cohort (Table 10, ERG report) representative of patient characteristics for people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency?	The RWEQ cohort does have differences compared to people with previously treated MMRd advanced or recurrent endometrial cancer. The clearest difference in the spectrum of histological subtypes. 42% of the RWEQ cohort had endometrioid type endometrial cancers compared to 66% of the GARNET trial ITT population. In contrast, the incidence of serous cancers was 40% (RWEQ) versus 4% (GARNET). This difference is driven by the distinct molecular biological profiles of endometrial cancer histologies whereby MMRd if seen most commonly in endometrioid cancers and rarely is serous cancers. The other difference is that the RWEQ cohort is less heavily pretreated as all patients had only received one prior line of chemotherapy whereas 37% of the GARNET ITT population had received at least 2 prior lines. More intensive pretreatment is generally considered a poor prognostic factor in solid tumours. Although there are no large datasets reporting the outcome of standard second-line therapy in recurrent endometrioid endometrial cancer (as a surrogate for MMRd disease), it should be noted that the PALEO trial (Mirza et al ESMO annual meeting 2020 LBA28 https://doi.org/10.1016/j.annonc.2020.08.2258), a randomised phase II trial comparing letrozole to letrozole+palbociclib recruited 77 patients with oestrogen receptor positive advanced/ recurrent endometrioid endometrial cancer which had failed one prior line of systemic therapy. Median PFS in the arm receiving letrozole alone was 3.0 months. This confirms the limited efficacy of second-line therapy (and endocrine therapy specfically) in this patient group.
Are the patient characteristics in the ZoptEC (Table 40, company submission, appendices) representative of	The ZoptEC control arm (doxorubicin-treated) patient characteristics also has a greater proportion of women with serous carcinoma (25%) than would

patient characteristics for people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency?	be anticipated for people with previously treated MMRd advanced or recurrent endometrial cancer. Otherwise, I think it is fairly representative in terms of other demographic characteristics.
What proportion of people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency would be expected to be progression-free at 3,5,10,15 and 20 years following treatment with dostarlimab?	This question (and the subsequent 4 questions) are very difficult to answer with a high degree of confidence due to the limited follow-up data available from the GARNET trial. However, what is clear from GARNET and other phase II trials of immune checkpoint inhibitors in an appropriately biomarker selected population of patients with advanced/ recurrent endometrial cancer after failure of platinum-based chemotherapy is that the duration of documented responses, is much longer than that seen with standard-of-care chemotherapy. In GARNET, 45% of patients had disease that responded to dostarlimab and 89% of these were still in response after a median of 16.3 months FU. The 2 comparator trials of immune checkpoint inhibitors discussed in section 3.5.1 of the ERG report are not the most appropriate studies to evaluate as patients entering these trials were not selected on the basis of MMR or MSI status, hence I would not expect the majority of patients in these trials to gain benefit from an immune checkpoint inhibitor. There are however 3 non-randomised phase II trials which do include cohorts of women with MMRd/ MSI-H advanced/ recurrent endometrial cancer which do provide a more relevant comparison. Antill et al (J Immunother Cancer 2021;9:e002255. doi:10.1136/jitc-2020-002255) report the outcomes of the PHAEDRA trial in which a cohort of 35 patients with MMRd advanced/recurrent endometrial cancer and another cohort of 36 patients with MMR proficient disease were treated with the anti- PDL-1 monoclonal antibody, durvalumab. Histology in

	MMRd versus MMRp included endometrioid (94% vs 57%) and serous (0% vs 31%). Objective response rate in the MMRd cohort was 47% vs 3% in the MMRp cohort (1/35, 95% CI 1 to 15, PR). Median progression-free survival was 8.3 months in the MMRd cohort vs 1.8 months in the MMRp cohort. The 12-month overall survival (OS) rate was 71% in MMRd vs 51% in MMRp, with median OS not reached for MMRd vs 12 months for MMRp. Notably only 2 of the 18 patients with a response to avelumab had experienced disease progression by the end of trial data collection (median FU on 19 months for MMRd cohort). Konstantinopoulos et al (J Clin Oncol 2019 37;2786-94) treated thirty-three patients with recurrent/ persistent endometrial cancer with avelumab (an anti-PDL-1 monoclonal antibody). Sixteen had MMRp disease and 17 MMRd disease. In the MMRp cohort only one of 16 patients exhibited a response. The MMRd cohort met the predefined primary end point of four OR. Of 15 patients who initiated avelumab, four exhibited OR (26.7%) and six were progression-free at six months (40.0%). Of most relevance is the endometrial cancer cohort recruited to the KEYNOTE158 trial (Marabelle et al J Clin Oncol 2019 38; 1-10). This phase II trial recruited patients with advanced/ recurrent non-colorectal MMRd cancers who had failed prior therapy. Patients received pembrolizumab (a monoclonal anti-PD-1 antibody) for a maximum of 2 years or until disease progression/ unacceptable toxicity. At the time of data cut-off. Median FU was 13.4 months. 49 patients with MMRd endometrial cancer were recruited and 28 (57%) has a documented disease response to treatment. Median PFS was 25.7 months and median duration of response was not reached. Importantly, the data for an expanded patient cohort from this trial was updated at the ESMO Annual meeting in September 2021 (O'Malley et al abstract 795MO https://doi.org/10.1016/j.annonc.2021.08.1237). Efficacy was assessed in the the 79 patients who received at least 1 pembrolizumab dose and had at least 26 wks follow up. Median follow-up was 42.6 months for this group. Overall

	response rate was 48% and median PFS was 13.1months. In those patients with a disease response, 88% had a least 1 year response duration, 73% at least 2 years and 68% at least 3 years. This confirms that there is significant plateauing of the PFS curve with mature 3year PFS rate of 37% and 3 year OS of 60% reported. Taking into account these studies and the GARNET data, my best estimate is that 35% of patients treated with dostarlimab would be progression-free and 3 years and 28% at 5 years. Predicting beyond that timepoint is very difficult but it is likely that there would be a slow increase in the numbers of patients with disease progression.
What proportion of people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency would be expected to be alive at 3,5,10,15 and 20 years following treatment with dostarlimab?	My best estimates are 3 year OS- 50%, 5year OS-35%.
What proportion of people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency would be expected to remain on treatment with dostarlimab after 1, 2,3, 4, and 5 years?	My best estimates are 1 year 40%, 2 years 25%, 3years 10%.
Due to treatment waning, what would you expect the	I do not have sufficient expertise to answer this question. However, the newly

treatment efficacy to decrease by in people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency at after 1, 2,3, 4, and 5 years after dostarlimab cessation?	presented data from the KEYNOTE 158 trial where pembrolizumab was stopped at 2 years does not indicate any clinically relevant waning in activity at the 3year timepoint.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Dostarlimab provides a novel biomarker-driven therapy for patients with advanced/ recurrent endometrial cancer who have failed first-line chemotherapy
- In MMRd advanced/ recurrent endometrial cancer, dostarlimab treatment was associated with a response rate of 45%
- Responses to dostarlimab were extremely durable with 80% of response still ongoing at 18 months. This is likely to translate through to a substantial improvement in survival for this patient group
- Dostarlimab is generally well-tolerated. UK centres are well-equipped to manage immune-related toxicities promptly and effectively
- The introduction of dostarlimab to the treatment portfolio of advanced/ recurrent endometrial cancer would be a step-change in management for patients with this difficult to treat disease where there is currently no defined standard-of-care.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **16 September**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency and current treatment options	
About you	
1.Your name	**Hilary Maxwell**
2. Are you (please tick all that apply):	☐ a patient with advanced or recurrent endometrial cancer? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with advanced or recurrent endometrial cancer? ☐ a patient organisation employee or volunteer? ☐ other (please specify): Gynae-Oncology Clinical Nurse Specialist. Chair of Nursing Forum/BGCS
3. Name of your nominating organisation.	GO Girls
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement

	☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with advanced or recurrent endometrial cancer? If you are a carer (for someone with advanced or recurrent endometrial cancer) please share your experience of caring for them.	N/A

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for advanced or recurrent endometrial cancer on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Treatments for women with advanced endometrial cancer are severely limited. Whilst in many cases, endometrial cancer has a high survival rate due to early detection, there is a considerable unmet need for women with advanced endometrial cancer. Treatment has been limited to conventional chemotherapy (carboplatin/paclitaxel) with very limited effect. There are simply no alternatives for these women and their outlook is bleak. In effect, there are equality and ethical issues here. We are only able to offer women one type of treatment, chemotherapy, knowing that the prospect of it working is low. This makes it a “no choice” situation for women who may be desperate to extend life with some cancer treatment than none. Offering a realistic alternative would give women that choice and meet this unmet need as well as for the first time offering a real time opportunity to extend progression free survival (PFS).
8. If there are disadvantages for patients of **current NHS treatments** for advanced or recurrent endometrial cancer (for example how dostarlimab is given or taken, side effects of treatment etc) please describe these	Women who require ‘standard’ chemotherapy may expect to give up a whole day to chemotherapy transfusions. Dostarlimab has an advantage of being a 30 minute infusion; this therefore has cost benefits to hospitals/clinics offering this treatment and considerable benefits to patients where time is critical to them.

Advantages of this treatment	
9a. If there are advantages of dostarlimab over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does dostarlimab help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	The biggest advantage to women is offering a treatment which currently does not exist; where we know current treatment is not effective and offers little hope. This treatment would enable women to have a much more effective functioning life being able to resume and maintain activities they would not normally be able to, thereby improving their QOL. As a result many women are working until retirement age and if improved treatments enable them to continue a working life and contributing to the economy and society this has whole societal benefits, as well as enabling women to retain their identity. Dostarlimab therefore meets an unmet need for such women; what is sad is that there are many women before them who would have benefited from this treatment who have now sadly passed away.
Disadvantages of this treatment	
10. If there are disadvantages of dostarlimab over current treatments on the NHS please describe these? For example, are there any risks with dostarlimab? If you are concerned about any potential	Compared to current chemotherapy treatment, there are no significant disadvantages of dostarlimab, only potential benefits.

side affects you have heard about, please describe them and explain why.	
Patient population	
11. Are there any groups of patients who might benefit more from dostarlimab or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Endometrial cancer often affects an older population. However, many are still of working age and therefore offering a treatment which is effective and .
Equality	
12. Are there any potential equality issues that should be taken into account when considering advanced or recurrent endometrial cancer and dostarlimab? Please explain if you think any groups of people with this condition are particularly disadvantaged.	In rural settings there is often considerable travelling for patients for treatment. As an example, in the South West, a patient may need to undertake a round trip from Lyme Regis to Dorchester (70 miles) when a) unwell b) older. This will apply to many rural settings across the UK This has significant implications for rural communities. Women and their families may not drive, nor have access to good public services and many of these services are infrequent and untimely. There is also a considerable cost to these patients. This disadvantages these groups considerably. A shorter treatment option could be delivered by clinical teams closer to home in community hospitals in the way in which we manage blood transfusions in the

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	community. By default, women as a group are disadvantaged if there is only one treatment option available to them and no other choices, they are being disadvantaged by saying “you only have one choice and that has not been proven to work well”.
Other issues	
13. Are there any other issues that you would like the committee to consider?	This is the first time in many years that an appropriate alternative is being recommended to women with advanced endometrial cancer; this meets a significant unmet need for women and addresses inequalities towards women with endometrial cancer.

	With all women now being tested for MMR/MSI, we are likely to see more women benefitting from this drug.

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: The patient population specified in marketing authorisation and addressed in the company submission (CS) is narrower that what is specified in the final scope	It is likely the population grouping is inevitably larger. It is not long since all hospitals have been required to undertake MMR/MSI testing on all endometrial cancer cases. Endometrial carcinoma is the commonest gynaecological cancer in the developed world with a rising incidence in postmenopausal women. In the UK it is the 4th most common cancer in women.

Key issue 2: Patients with advanced disease and with recurrent disease are potentially two distinct populations, but they were identified in different ways between the GARNET trial for dostarlimab and the GARNET-like Real World EQuivalent (RWEQ) cohort	They were identified differently. As stated in the ERG, there are comparables to the two groups. However, FIGO III and IV disease equate to advanced disease at outset. The likelihood of recurrence therefore is much greater, in effect, making the disease advanced. To a patient, options in recurrent disease *with* advanced endometrial cancer is important to meet an unmet need.
Key issue 3: Overall the GARNET trial data were fairly immature and may not be sufficient to provide reliable effectiveness and cost-effectiveness estimates	Longer-term data should be collected. As with all trials, evidence can only be sourced on the longevity of a drug under trial. What is important is the efficacy within timeframes whether short or long as it would be anticipated this would be mirrored as more evidence is collected.
Key issue 4: There are uncertainties over the magnitude of the benefit of dostarlimab relative to comparators due to the single-arm design of the GARNET trial and lack of suitable data for comparator treatments	Ultimately a randomised controlled trial would provide non-biased data. On the current evidence as it exists, this does not necessarily make dostarlimab an ineffective comparator.
Key issue 5: GARNET trial population and RWEQ cohort may have fundamental differences that cannot be easily adjusted statistically	This is difficult because these are two different trials with two different parameters. Ultimate resolution will still lie with a randomised controlled trial. However, based on the research data that exists, it is possible to analyse parallels in both trials to extrapolate comparators, albeit not an exact comparable.
Key issue 6: Model errors	No further comment to what has been suggested.

Key issue 7: Dostarlimab overall survival (OS) elicitation exercise and choice of OS curve	Not qualified to comment.
Key issue 8: RWEQ OS elicitation exercise and choice of OS curve	Not qualified to comment
Key issue 9: Dostarlimab time to treatment discontinuation (TTD) elicitation exercise and treatment discontinuations	Not qualified to comment.
Key issue 10: Dostarlimab choice of TTD curve	Not qualified to comment.
Key issue 11: Censoring and the possibility of informative censoring	Not qualified to comment.
Key issue 12: Reliability of comparing GARNET with the RWEQ	Agree this could be extrapolated from ECOG performance status.
15. Are there any important issues that have been missed in ERG report?	This is an unmet need for women to have a choice to have access to a drug which holds current evidence to support improved PFS.

Additional technical team questions	
Does prognosis differ between people with advanced endometrial cancer and those with recurrent endometrial cancer?	This is a very difficult question to answer as there are so many influencing factors that affect prognosis. I don't think this question is helpful when deciding whether a new treatment will be of benefit. The benefit come from ensuring an unmet need is met, continued data collection on PFS (together with performance status) and reducing inequalities in healthcare treatments for women with endometrial cancer.
What would be the expected overall survival time for people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency from the start of next-line dostarlimab?	See above.
Are the patient characteristics in the GARNET ITT trial (Table 10, ERG report) representative of patient characteristics for people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency?	Yes.
Are the patient characteristics in the GARNET-like UK RWE (RWEQ) cohort (Table 10, ERG report) representative of patient characteristics for people with previously treated	Yes

advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency?	
Are the patient characteristics in the ZoptEC (Table 40, company submission, appendices) representative of patient characteristics for people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency?	It is hard to comment fully. Again, there are many variables that may have contributed to death whilst patients remain in the study; not least probably age is the most significant factor.
What proportion of people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency would be expected to be progression-free at 3,5,10,15 and 20 years following treatment with dostarlimab?	There currently is insufficient data to answer this; this needs to be completed prospectively and should form part of on-going assessment for dostarlimab.
What proportion of people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency would be expected to be alive at 3,5,10,15 and 20 years following treatment with dostarlimab?	There currently is insufficient data to answer this; this needs to be completed prospectively and should form part of on-going assessment for dostarlimab. Please also note it is only a short time since hospitals have been collecting data on MMR/MSI, so this information does not yet have longevity.
What proportion of people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability	There currently is insufficient data to answer this; this needs to be completed prospectively and should form part of on-going assessment for dostarlimab, but hopefully a high proportion, although

or mismatch repair deficiency would be expected to remain on treatment with dostarlimab after 1, 2,3, 4, and 5 years?	other factors will impact.
Due to treatment waning, what would you expect the treatment efficacy to decrease by in people with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency at after 1, 2,3, 4, and 5 years after dostarlimab cessation?	Not qualified to comment.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Women with recurrent endometrial cancer and/or advanced disease have no other alternative treatments other than standard chemotherapy which is well known not to be effective in this grouping.
- Dostarlimab has been approved by the European Medicines Agency (EMA) in April 2021
- Dostarlimab meets an unmet need for patients with recurrent and/or advanced disease.
- Access to Dostarlimab would help address the health inequalities for women who are significantly disadvantaged to having access to only one type of treatment currently, chemotherapy with minimal success.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]

ERG critique of company technical engagement (TE) response

Produced by *Warwick Evidence*

Date completed *5 October 2021*

Please note that: Sections highlighted in [redacted] are '[redacted]',
and sections highlighted in [redacted] are [redacted]

Key Issue 1:

No comment.

Key Issue 2:

The ERG's primary concern is that different definitions for patients with advanced disease and recurrent disease were used in the GARNET trial and the GARNET-like Real World EQuivalent (RWEQ) cohort. As a result, patients were selected into the GARNET trial and the RWEQ cohort in a different and important way. The provision of subgroup data using a more consistent definition across the GARNET trial and the RWEQ could have enabled subsets of GARNET and RWEQ data representing more comparable subgroups to be generated for a less biased comparison. The unavailability of such data means that systematic differences between GARNET ITT and RWEQ data (which do not seem to be amenable to adequate adjustment using matching-adjusted indirect comparison as highlighted in Section 3.4 of the ERG report) and potential bias associated with the differences remain in comparisons based on these sets of data.

Key Issue 3:

The ERG maintains that data currently available from the GARNET trial are insufficiently mature, and that collection of longer-term data from a randomised study with suitable comparators and/or a dostarlimab-treated cohort that better matches the characteristics of patients seen in UK clinical practice would substantially reduce decision uncertainty.

Key Issue 4:

No further comment (but see ERG's response to Key issue 3 above).

Key Issue 5:

The ERG appreciates the company's provision of data on endometrioid subgroups. The company re-classified 5 patients with histological features related to adenocarcinoma in the GARNET trial from non-endometrioid to endometrioid group during the data preparation process (p.9, company TE response). The reclassification may be reasonable if it improved consistency in the classification of patients between the GARNET and RWEQ cohorts, although the ERG cannot assess this as detailed classification criteria were not presented.

While the endometrioid subgroup data mitigate one of the major differences between GARNET and RWEQ, the ERG notes that (even within this more homogeneous subgroup of patients) substantial

differences in patient characteristics between the two datasets remain. Key differences include ECOG performance status, FIGO stage, disease grade, number of prior platinum-based therapies in the advanced/recurrent setting and surgery for advanced or recurrent endometrial cancer (see Table 1 below).

Table 1: Differences in patient characteristics between GARNET and RWEQ endometrioid subgroups (reproduced in part from company TE response Table 1, p.10-11)

Baseline characteristics	Dostarlimab (GARNET endometrioid cohort) (N=[redacted])	Current clinical management (RWEQ endometrioid cohort) (N=[redacted])
Age category		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
<65 years	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]
ECOG performance status at index		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
FIGO Stage at initial diagnosis		
Stage I	[redacted]	[redacted]
Stage II	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]
Disease grade at initial diagnosis		
Grade 1/2	[redacted]	[redacted]
Grade 3/4	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Number of prior platinum-based therapies in the advanced/recurrent setting		
0[a]	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3[b]	[redacted]	[redacted]
Surgery for advanced or recurrent endometrial cancer		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Footnotes: [a] One patient was recorded as having had 0 line of platinum-based therapy per the GARNET methodology, with a protocol deviation because an adequate duration of time was not present between the prior anticancer therapy and the first administration of dostarlimab. [b] One patient is recorded as having three lines of prior platinum-based chemotherapy, which included treatment in the neoadjuvant/adjuvant setting. The GARNET trial protocol stipulated that patients had to have received no more than 2 lines of anti-cancer therapy for recurrent or advanced (≥Stage IIIB) disease. Any treatment a patient received for early stage disease would not have fallen into this criterion.

Abbreviations: ECOG: Eastern Cooperative Oncology Group; FIGO: Federation of Gynecology and Obstetrics; ITT: Intention to treat; RWE: real-world evidence; RWEQ: real-world equivalent;

Major issues associated with ECOG performance status include missing data for half of the patients in RWEQ cohort and the different timing at which performance status was assessed: at study entry for GARNET (which was very close to the start of dostarlimab treatment) and at registry entry for RWEQ (with varied duration of time elapsed before the patients received the comparator treatments). It is therefore not possible to evaluate comparability of patients between the two patient cohorts with regard to this important factor which is potentially prognostic. For FIGO stage at initial diagnosis, a higher proportion of patients in GARNET had earlier stage of disease than in RWEQ, which potentially biases in favour of dostarlimab. Similarly, substantially higher proportion of patients in GARNET had lower grade cancer, again potentially biases the comparison in favour of dostarlimab.

The company stated that the endometrioid subgroup of patients in GARNET were older, and 11.1% of them had 2 or more prior platinum-based therapies compared with all patients having received only one prior platinum-based therapy in RWEQ, and suggested that these were likely to introduce bias in favour of comparator treatments (p.15 of company TE response). The ERG disagrees. Firstly, as shown in Table 1 above, the difference in age between GARNET and RWEQ endometrioid subgroups was fairly minor. Secondly, patients with greater number of prior treatments do not necessarily have less favourable prognosis as survivor effect needs to be taken into account.

The overall survival (OS) and progression free survival (PFS) for the GARNET endometrioid subgroup tends to be similar or slightly worse compared with the GARNET ITT (except for PFS at 18 months, see Table 2 and Table 3 of the company TE response). This was unexpected as patients with endometrioid histology are generally associated with better prognosis. By contrast, the RWEQ endometrioid subgroup tends to show better OS and PFS compared with the RWEQ all patient cohort (as would be expected). The net effect of excluding non-endometrioid patients was a smaller estimated survival advantage for dostarlimab versus comparator treatments (OS for naïve comparison, 0.39 for all patients vs 0.48 for endometrioid). The divergent effects of excluding non-endometrioid patients observed between GARNET and RWEQ is a further indication of fundamental differences between the two cohorts that would be difficult to reconcile by statistical adjustments.

To sum up, while the endometrioid subgroup data removed potential confounding arising from difference in histological type between GARNET and RWEQ, major differences in patient characteristics remain in this subgroup of patients. Consequently, while comparisons made using the

subgroup data may have removed some bias and indeed the observed effect sizes became smaller as expected, the comparisons were still likely to be subject to substantial degree of potential bias. The matching-adjusted indirect comparisons carried out by the company for the subgroup data do not appear to adequately address these issues, and therefore the relative effectiveness for dostarlimab vs comparators estimated from the endometrioid subgroup is still associated with high level of uncertainty, and is likely to be an over-estimate.

The company provides an ICER restricted to the endometrioid patient group. The ERG does not view this ICER as relevant to the AC decision making in terms of making recommendations for a particular subgroup. The ERG motivation for considering the endometrioid subgroup is to increase the comparability between the GARNET data and the RWEQ data, and so to explore the uncertainty and possible bias around the all-patient comparison. As noted above, the clinical effectiveness estimate for dostarlimab in the endometrioid subgroup tends to be worse than for all patients which may suggest that the RWEQ all patient group may perform unduly poorly so biasing the all-patient analysis clinical effectiveness estimate. The ERG thinks this may be due to a mismatch between the non-endometrioid patients in GARNET compared to the RWEQ.

With regards the economics the company presents two main sets of ICERs for the endometrioid subgroup: one based upon applying a hazard ratio: Company TE response page 17: Scenario 3 with an ICER of £48,614 per QALY, and one upon the naïve comparison: Company TE response page 17: Scenario 5 with an ICER of £55,626 per QALY.

The company base case for the all-patient analysis adopts the naïve comparison methodology that mirrors Scenario 5. It has an ICER of £48,608 per QALY. The ERG thinks that this can only be meaningfully compared with the endometrioid Scenario 5 ICER of £55,626 per QALY. Mirroring the worse clinical effectiveness estimate for the endometrioid subgroup compared to the all-patient group, the relevant ICER worsens by 14%.

1. The concentration upon the naïve comparison is supported by the company base case methodology, and the company TE response which states "*The use of hazard ratios to derive comparator efficacy estimates versus dostarlimab is inappropriate, given the fundamental differences in mechanism of action between dostarlimab and chemotherapies, and likely violations of the PH assumption. Deriving comparative efficacy estimates by independently fitting extrapolations to both arms represents a more appropriate approach*".
2. The company ICER for the endometrioid patient group is based upon endometrioid subgroup specific OS and PFS data and curves. But it appears to apply the all-patient ToT curves. The ERG does not know why the company did not update the ToT curves to be endometrioid

subgroup specific. The ToT curves are central to estimating the dostarlimab direct drug costs and so are key inputs to the ICER. As a consequence, the endometrioid ICERs of the company TE response are biased. The ERG does not know the extent and direction of this bias.

Key Issue 6:

The company largely accepts the modelling errors identified by the ERG. Areas of disagreement remains.

1. The company rejects the ERG application of the GARNET 1.4 average number of post-dostarlimab treatments among those receiving a subsequent treatment. This is due to uncertainty around the estimate, that it was generated during a global trial so may not be relevant to the UK and that the multiplier is not applied in the comparator arm. The ERG thinks that GARNET trial provides a reasonable estimate, that the GARNET OS data reflects this treatment pattern and that there are reasons to think that the average number of treatments after dostarlimab will be higher than the average number of treatments after the initial RWEQ treatment. The ERG retains the approach of the original ERG report. The effects upon the ICER are minor.
2. The company rejects the ERG assertion that there should be consideration of cisplatin + doxorubicin on the grounds that the RWEQ percentage receiving it of 4.9% is below the company imposed 5.0% cut-off. The ERG notes that this difference is very marginal and that the other RWEQ treatments with less than 5.0% of patients have very much fewer patients than cisplatin + doxorubicin. As per the original ERG report, the ERG also notes that the effect upon costs of including cisplatin + doxorubicin within the basket of RWEQ treatments that are costed is very small. The main ERG concern around the company exclusion of cisplatin + doxorubicin is that it means that the company has not presented the clinical effectiveness data for cisplatin + doxorubicin in a like manner to that supplied for the other comparators within the RWEQ costing basket. The ERG remains of the opinion that it would have been better to have presented this data. The effects upon the ICER are minor.
3. The company rejects the ERG preference for the utility model without the time to death variable. No new arguments are presented by the company, the arguments of the original ERG report section 4.3.4.1 still apply and the ERG remains of its original opinion. The effects upon the ICER are minor.

The main company modelling innovation at TE appears to be an attempt to revise the ERG implementation of the waning of treatment effect. The company under its response to Key Issue 9

states that "*Using the ERG's methodology, a patient who discontinues dostarlimab after [redacted] years of treatment is assumed, at [redacted] to immediately transition to a hazard of death equal to the hazard of death at the same timepoint for a patient who initially started treatment with current clinical management*." The ERG thinks that this is probably a typo and should read "*Using the ERG's methodology, a patient who discontinues dostarlimab after [redacted] years of treatment is assumed, at [redacted] to immediately transition to a hazard of death equal to the hazard of death at the same timepoint for a patient who initially started treatment with current clinical management*." This correctly reflect the arithmetic of the ERG waning, which the company accepted at FAC and which reflects the waning that the original company submission intended to apply; i.e. equalisation of hazards at 5 years.

The company method reportedly seeks to apply something akin to the ERG method but to apply it for [redacted] years for those ceasing treatment at [redacted]; i.e. to extend the treatment effect of dostarlimab out to [redacted] years.

This is to confuse the cessation points of 2 years and 5 years with clinical evidence of retention of benefit for [redacted] years after cessation of treatment. This was never the intention of the ERG method. The ERG method is a simple weighted average to get from the hazard of the dostarlimab parameterised curve at year [redacted] to the hazard of the RWEQ curve at year [redacted], when all cease treatment. The weight for the RWEQ hazard increases linearly over this period from 0% to 100%. This is not untypical of modelling where there is a starting point and an end point which are well defined, with a simplifying heuristic to get from one to the other. This is as per the stated intention of the original company submission. Neither imply that the benefit of dostarlimab endures for 3 years after treatment cessation, and any conclusions from this are hung on a modelling artefact and are not grounded in any clinical evidence.

There is a question about the duration of retention of benefits after cessation of dostarlimab treatment. The assumed cessation points of [redacted] and [redacted] years within the model do not provide anything that answers this question. Indeed, they are entirely irrelevant to it.

It can be noted that the company revision to the ERG method has, for the company revised base case, little effect: the ICER is only improved by £1k per QALY. The ERG cautions that this effect on the ICER may increase if the proportions modelled as remaining on treatment between year [redacted] and year [redacted] increase. Time constraints, the late availability of the company TE model and the company waning method not being obviously implementable within the submitted TE model mean that the ERG has not cross checked the company method. Because the company method has not been clearly set out in the electronic model, has not been verified as correct and previously had a major modelling error

in its implementation, coupled with the apparently limited effect it has upon the ICER and the uncertainty about the duration of retention of benefits, the ERG retains its method.

Key Issue 7:

ERG critique of parametric modelling of OS in GARNET

For modelling OS in GARNET the company follows a procedure with four elements:

A] Exploration of parametric models, presenting them superimposed on KM analysis to illustrate visual fit. B] Select a parametric model on the basis of lowest sum of IC scores (AIC + BIC). C] Adjust the parametric model for waning of treatment effect and so as not to exceed OS of general population. D] Adopt an adjusted parametric model that best reflects and conforms to the predictions of clinical experts consulted by GSK.

Taken as a whole the company procedure selects a required pre-determined result (clinicians' predictions) and adopts method(s) that will generate it, rather than select method(s) and then determine the result. This is essentially a teleological approach (result dictates model, rather than model dictates the result). It relies on the assumed accuracy/reliability of clinicians' predictions and renders the adopted methods difficult to test independently implying that several different method(s) that generate the desired pre-determined result are acceptable. The company have used the outcomes vs. time data in mathematical modelling that has only the appearance of validity since the mathematics is made to fit the pre-determined outcome. The clinical predictions are probably best regarded as informed speculations. The information provided clinicians was for 129 patients in GARNET; according to binomial distribution a predicted proportion based on information on 129 is associated with wide 95% CIs relative to information for 1290 as illustrated in Figure 1.

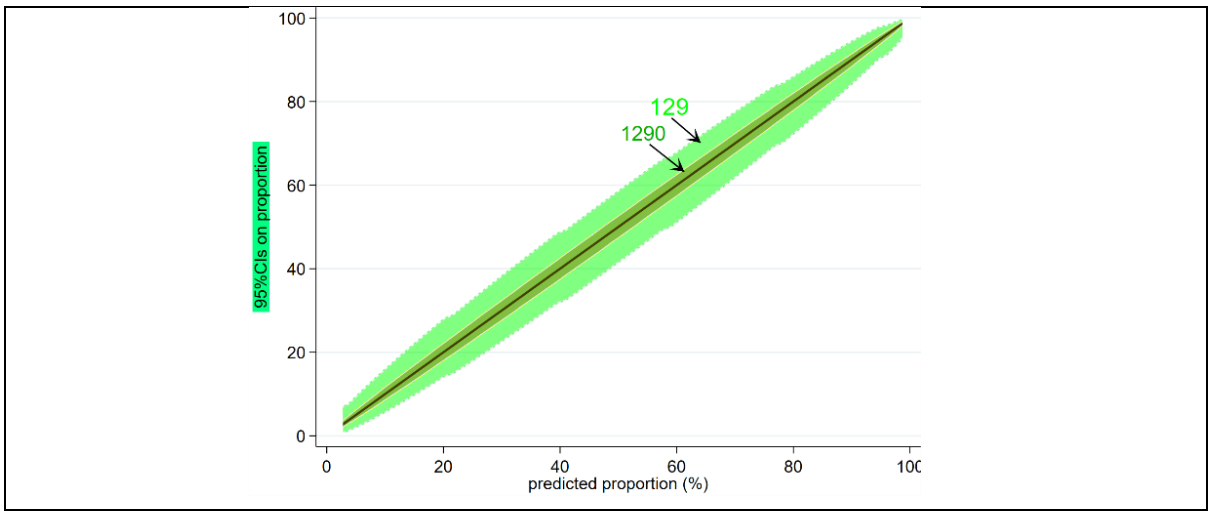

Figure 1 Binomial CIs associated with predicted proportions

The ERG has several additional concerns: (i) the clinicians' predictions varied between individual clinicians and are associated with considerable uncertainty that is not accounted for in the company TE response analysis; consulting a larger or different set of clinicians could result in a considerably different mean of predictions implying that alternative selection of parametric models to those currently favoured would be judged "best" fit; no evidence is presented for an example where clinician predictions have been vindicated by subsequent data; here there is no available test of prediction accuracy; (ii) the parametric methods that are used to generate the pre-determined results are associated with major "mathematical" uncertainties not accounted for in the company TE response. It is of note that since no specific clinicians' predictions are available for the endometroid subgroup (company TE response Appendix 1) the company approach seems difficult to apply for this subgroup.

In the section below the individual elements of the company procedure are considered in turn.

A] The company have explored a comprehensive range of parametric models but visual fit is relatively poor. The KM plot does not reach a median, exhibits several changing trajectories and a long flat tail. In ERG opinion immaturity of data is due to too short follow up, too few participants, and too few events relative to number of participants. Longer follow up could mitigate this problem.

B] The company have again selected a ggamma model for GARNET OS on the basis of sum of IC scores. This model does indeed score the lowest IC sum. The ggamma does score better than the Weibull on basis of AIC and BIC. However, because of paucity in the data all models are associated with considerable uncertainty (not considered in the company TE response) illustrated in the ggamma OS model's 95% CIs (Figure 2A). The Weibull model has narrower 95% CIs, probably being less influenced by the flat tail. The wide 95% CIs of different models of OS largely overlap in the observation period that the company use for waning adjustment (Figure 2B). The considerable uncertainties mean there is not a strong case for selection of one model in preference to another. The ggamma predicts survivors well beyond 30 years and does not seem reasonable to the ERG.

Figure 2: KM plot of GARNET OS and unadjusted parametric models with 95% CIs (to 20 years)

Similarly, except for the first couple of months of follow up, the 95% CIs around ggamma and Weibull modelled hazards overlap for most of the first year (Figure 3). The smoothed non-parametric hazard of GARNET OS data (Figure 3) reflects the multiple changes in trajectory seen in the KM plot; there seems little difference between ggamma and Weibull models' 95% CIs in their capacity to accommodate these changes.

Figure 3: Figure XX+1 Non-parametric and parametric modelled hazards with 95% CIs.

Somewhat misleadingly the company state that the ggamma model represents the "best statistical fit". The choice of ggamma is based on IC scores and there is no existing statistical test available to discriminate between IC scores (hence the use of sum of scores has been used by the company).

C] New adjustment method for waning of treatment effect

Figure 4 New and previous waning-adjusted ggamma and Weibull models compared with unadjusted models

The company have introduced a new adjustment for waning of treatment effect and have applied this to parametric models. Relative to the previous mode of waning adjustment this new method has had a very substantial influence on the resulting ggamma and Weibull models of OS, considerably reducing that for the ggamma model and slightly enhancing that for the Weibull after 6 years (Figure 4). The company correctly point out that the company's new waning adjustment to the Weibull model eventually (after 6 years) "unexpectedly" improves OS rather than reducing it, and conclude therefore that the Weibull model is inappropriate; however the ERG note that this happens only after ~86% of the patients have died and believe this result is rather due to a combination of the Weibull model with a somewhat arbitrarily selected method of waning that may or may not reflect reality and thus this does not invalidate the Weibull model. In order to explore the uncertainty inherent in the adjusted ggamma and Weibull models (below) the ERG have not allowed the waning adjusted model to provide superior survival to the corresponding unadjusted model.

Applying the new method of adjustment for waning has a very large influence on the ggamma model. The difference between adjusted models (ggamma vs. Weibull) is now greatly reduced

(relative to the previous waning method) and the ggamma model is more realistic but in ERG opinion is still optimistic in extrapolation (Figure 5).

Figure 5 Influence of waning adjustment on ggamma and Weibull unadjusted models taken with modification from the company's economic model

This substantial change in OS models resulting from type of waning employed illustrates how choice of waning method is driving the OS model and hence an economic analysis. The CTER favours the new waning adjusted ggamma OS model because it aligns with clinician's predictions; as explained above this is a teleological procedure. Whether the ggamma model is superior to the Weibull is difficult to judge because of the uncertainties associated with each model but not represented in the company's plots. Figure 6 and Figure 7 illustrate the large uncertainty in the waning-adjusted models when 95% CIs around the unadjusted models are taken into account.

Figure 6: Left: ERG estimates of 95% CIs around the company's waning adjusted GG model of OS; Right GG and Weibull waning models taken from company economic model. ***Note: it was not possible for the ERG to implement 95% CIs within the company's new economic model currently available to the ERG because there lacked a link between the "selected" parametric model for OS and the resulting adjusted model after the company's waning was applied.***

Figure 7: Left: ERG estimates of 95% CIs around the company's waning adjusted Weibull model of OS; Right Weibull waning model taken from company economic model. ***Note: it was not possible for the ERG to implement 95% CIs within the company's new economic model currently available to the ERG because there lacked a link between the "selected" parametric model for OS and the resulting adjusted model after the company's waning was applied.***

D] The company have selected the waning-adjusted ggamma model as best reflecting the predictions of clinicians and the results were summarised and compared vs. Weibull and ggamma models in CTER Table 7, reproduced as Table 2 below and modified by ERG to show differences between model and clinician prediction.

Table 2

	Proportion of patients predicted to be alive at each time point following treatment with dostarlimab, %		
Time	**Generalised Gamma**	**Weibull**	**Mean clinical expert estimates**
3 years			
5 years			
10 years			
15 years			
20 years			

While the ggamma model is marginally closer to the mean of clinicians' predictions the ERG is concerned that the substantial uncertainty in the parametric models (Figure 6 and Figure 7) is not represented in the values in Table 2, and similarly that the variation between individual clinician's predictions and the uncertainty inherent any individual prediction (examined in the previous ERG report) is also not represented. Together these uncertainties indicate that there is insufficient difference between these two models for one to be selected in preference to the other if judged against the predetermined expectation of clinicians and therefore in the ERG opinion company's conclusion should be viewed with a high degree of caution.

Conclusion for modelling dostarlimab OS

The company's modelling of OS is associated with very substantial uncertainties both before and after adjustment for waning of treatment effect. The company's decision to adopt the ggamma model's central estimate (and not explore associated confidence intervals) does not fully reflect the associated uncertainties with the modelling or the variation and uncertainty in clinicians' predictions. There seems no compelling reason to select ggamma modelling in preference to an alternative such as Weibull. From the evidence presented, the ERG consider the "true" survival of patients receiving dostarlimab lies somewhere within a wide range of possibilities and conclude that the company's estimate is too precise to be supported by the available data and likely overoptimistic since alternative plausible models generates lower estimates.

The ERG supplies additional scenario analyses that apply the upper and lower confidence limits of the curves in its main report, amended for Technical Engagement.

ERG critique of parametric modelling of PFS in GARNET

The company have followed the same procedural steps as for OS and these are subject to the same concerns already discussed for OS. The company have selected their waning adjusted loglogistic model for their base case analysis. In addition the company have decided: *"To investigate the impact that the potential underestimation of PFS has on the proportion of LYs and QALYs gained pre- and post-progression, the disaggregated LYs and QALYs from the Company's base case cost-effectiveness analysis are presented in Table 9 and Table 10, alongside the equivalent results when PFS extrapolation based on the Generalised gamma is used for dostarlimab"*. These results were presented in the company TE response Tables 9 and 10 and indicate a more even distribution of benefit between pre-progression and post-progression than previously modelled although a small

preponderance for post-progression still remains and the contrast with the control group (RWE) where pre-progression benefit predominates also remains.

In selecting the adjusted loglogistic model the company have not relied on the mean of clinicians' predictions as a guide to selection. The company have eliminated results for two clinician's ("outliers") to obtain a "*conservative*" clinician's mean prediction and compare this with loglogistic and ggamma output at a range of time points.

Figure 8: KM plot of GARNET PFS and unadjusted parametric models with 95% CIs (to 30 months)

The KM plot for PFS has an extreme shape with several trajectory changes. Both loglogistic, ggamma and other models of PFS are very poor visual fit particularly between 3 and 9 months and after 9 months, and they are associated with appreciable uncertainty (see Figure ***8*** above).

The company's new waning adjustment procedure has only a small influence in depressing the unadjusted PFS model plots (Figure 9).

Figure 9: Unadjusted and adjusted models of PFS (adapted from the company's economic model) Solid lines adjusted models dotted lines unadjusted models.

Incorporating the uncertainty associated with the unadjusted models is unlikely to substantially shift these adjusted curves.

In Figure 10 Hazard plots for loglogistic and ggamma models are compared with the non-parametric smoothed hazard plot based on the KM. In the ERG opinion both parametric models fail to follow the non-parametric hazard well and there does not appear to be compelling evidence to select one parametric in favour of the other.

Figure 10: GARNET PFS, non-parametric and parametric modelled hazards with 95% CIs.

Key Issue 8:

The ERG agrees that the most appropriate curve fitted to the RWEQ OS curve is the Log-logistic. This does not affect the ERG concerns about the RWEQ data set.

The company notes that the ERG gives greater credence to the company elicitation exercise for the RWEQ curves than to the company elicitation exercise for the dostarlimab parameterised curves. As reviewed in more detail in the man ERG report section 4.3.3.2:

- Within the model the RWEQ do not need to be adjusted for withdrawal of treatment at [redacted] years. As a consequence, it is valid to ask the experts what the presented KM curves may imply for OS and PFS, and which of the parameterised curve they think best fits the RWEQ data.
- Within the model the dostarlimab curves do need to be adjusted for withdrawal of treatment at [redacted] years. Apparently no mention was made of treatment withdrawal at [redacted] years during the morning session on survival estimates, this being subsequently covered during the afternoon session on patients numbers likely to remain on treatment. The company presented the unadjusted parameterised curves to the experts for assessment. This suggests that it did not anticipate the experts factoring in treatment withdrawal at [redacted] years. This is the reason the ERG gives less credence to the company elicitation exercise providing reasonable estimates for the OS and PFS estimates and the most appropriate dostarlimab parameterised curves for when the effects of treatment withdrawal at [redacted] years are factored in.

- Given the centrality of treatment withdrawal at [redacted] years to the modelling of the dostarlimab arm, the ERG cannot understand why this was not dealt with first in the morning session with this then feeding into an afternoon elicitation exercise about OS, PFS and parameterised curves for dostarlimab that takes into account treatment cessation and withdrawal of therapy.

The ERG agrees with the company that in the light of the company expert responses the RWEQ parameterised curves may be too pessimistic for the comparison that is being made. As a consequence, they may be biased in favour of dostarlimab.

Key Issue 9:

The company presents no new arguments. The cliff edge referred to by the ERG does not relate to the KM data but the modelled treatment pattern as per Figure 21 of the main ERG report.

The arguments of section 4.3.3.3 of the main ERG report still apply. The ERG remains of the opinion that the cliff edge of Figure 21 of the main ERG report may be too severe, the company elicitation exercise was biased in the data it presented and was leading in terms of the [redacted] "estimate". The ERG thinks that the company range of [redacted] is likely to be similarly biased, hence the midpoint of [redacted] too low. While not informed by any trial data, because of the bias in the company elicitation exercise the ERG thinks that a midpoint of [redacted] is reasonable for the base case, this also permitting symmetric scenario analyses that explore [redacted].

The ERG retains its correction to the original company waning for the reasons outlined under Key Issue 6 above.

The company notes that its two experts suggest that waning would start [redacted] after discontinuation and [redacted] after discontinuation. The company retains its assumption that the full treatment effect will be retained for [redacted] after cessation, providing a scenario and [redacted] retention of the full treatment effect. The ERG thinks that there remains uncertainty about this, but that the company experts most naturally suggest an input of [redacted]. [redacted] and [redacted] retentions of full treatment effect after cessation are covered by ERG scenarios 3a and 3b.

ERG expert opinion notes that the clinical consensus is that there is some retention of the full benefits from immunotherapy after treatment cessation but that there is no good evidence of when waning is of this benefit is likely to start and that there is no good evidence for a retention of benefits of [redacted] or for benefits to extend to [redacted].

Key Issue 10:

The ERG base case reflects the KM data that was supplied in answer to Clarification Question A6. The ERG parameterisation of the generalised gamma is virtually indistinguishable from the updated company analysis generalise gamma.

The ERG does not understand the argument that since GARNET did not have a stopping rule at [redacted] years, discontinuation rates using the best fitting generalised gamma are low after [redacted] years, so poorly represent "*real world prescribing of dostarlimab in the UK clinical setting*". The parameterisation of the KM data is trying to best fit the GARNET trial data, not some notional "*real world prescribing".*

The ERG thinks that the best parameterisation of the GARNET trial data should be applied, and assumptions about how UK prescribing would differ from this subsequently be applied to the chosen parameterisation: much as per the "*real world prescribing"* company assumptions around treatment withdrawal at [redacted] years and complete cessation at [redacted] years.

The company updated log-normal and generalised gamma TTD curves for dostarlimab correspond very closely with those of the ERG. The ERG has augmented the scenario analyses Table 54 of its main report to include the company updated log-normal TTD curve for dostarlimab.

Key Issue 11:

The company acknowledges that if the somewhat higher early drop out rate in GARNET compared to RWEQ had been observed in a two arm RCT it would be a major concern.

For the ERG the questions are: for the reasonably large proportion of patients who dropped out of GARNET quite early (1) who are they, and (2) what is likely to have happened to them in terms of progression and survival? Are they likely to have had a worse prognosis at baseline? Might they be likely to have a worse probability of remaining progression free and of survival as those who remained in GARNET, even if for no other reason than they are no longer receiving treatment? If so, applying estimates based upon the patients who remained followed up in the GARNET to all patients who enrolled in GARNET, including those who dropped out, may be biased.

If all had dropped out of GARNET before receiving any dostarlimab it can be argued that they could be ignored. But for most dostarlimab treatment costs will have been incurred for a period with uncertain long term benefits. A scenario applying the RWEQ hazards from the point of drop out to those dropping out early in the dostarlimab arm might be appropriate to give an upper bound to the ICER from consideration of this.

Key Issue 12:

Time constraints have limited how much of the additional company TE evidence and modelling that the ERG has been able to review. The ERG focusses upon the comparisons with doxorubicin using the ZopTEC trial and with PLD monotherapy using the RWEQ data. Table 15 of the company TE submission outlined the following differences from the company base case ICER of £48,608 for the various comparisons, the ERG augmenting this with the parallel percentage differences from the ERG base case based upon Table 55 of the main ERG report and the figures are shown in Table 3 below.

Table 3: Percentage change from the company base case ICER for various scenarios explored in the company TE response

	Waning to RWEQ pooled curve	Waning to individual Tx curve
Company analyses		
HRs derived from ZopTEC trial applied to dostarlimab unmatched GARNET curves.	-30%	12%
Curves fitted independently to dostarlimab GARNET MAIC KM data and to ZopTEC KM data.	+6%	+4%
Curves fitted independently to dostarlimab GARNET KM data and to RWEQ PLD treatment KM data.	+27%	+20%
ERG analyses		
Curves fitted independently to dostarlimab GARNET KM data and to RWEQ PLD treatment KM data.	+33%	+27%

The company largely discounts the first set of analyses based upon applying hazard ratios for methodological reasons. This leaves:

- The ZopTEC trial fitted curve ICERs which suggests little change to the company base case ICER, and
- The comparison based upon fitting curves independently to GARNET and the RWEQ PLD monotherapy data which in contrast suggests a considerable improvement in the ICER.
- The ERG estimates based upon fitting curves independently to GARNET and the RWEQ PLD data which broadly mirror the effects for of the parallel company analyses.

This would seem to bolster rather than contradict the ERG argument that an analysis of an individual treatment based upon trial patient populations, GARNET and ZopTEC, results in a worse ICER than an analysis based upon comparing a trial population, GARNET, with a retrospective observation based population, the RWEQ.